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ANKARA MEDICAL JOURNAL

# From the Editor

Dear Readers,

Welcome to the first edition of 2026! We are delighted to present this carefully curated collection of articles designed to engage and inspire healthcare professionals, with a particular focus on our valued primary care physicians. Our commitment to providing essential guidance in navigating the ever-evolving healthcare landscape remains steadfast.

In this issue, you will find nine research articles and two case reports, each offering meaningful insights into recent developments and practical challenges in critical areas of healthcare.

As Türkiye's leading primary care journal, we take pride in our role as a trusted resource for healthcare professionals across the region. Your continued interest and support strengthen our dedication to delivering up-to-date, evidence-based knowledge relevant to primary care practice.

We invite you to explore the insightful and thought-provoking contributions featured in this issue. We are confident that they will both inspire and inform your clinical practice. Your engagement remains central to our mission of advancing knowledge and innovation in primary care.

Stay tuned for our next issue, which promises to be equally enriching and impactful.

**Prof. Dr. Ahmet Keskin**

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Research Article

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# CIRCADIAN BLOOD PRESSURE PHENOTYPES AND 24-HOUR VARIABILITY AS DETERMINANTS OF MENTAL HEALTH-RELATED QUALITY OF LIFE IN HYPERTENSION WITH TYPE 2 DIABETES AND OBESITY

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## Abstract

**Objectives:** Multimorbidity combining hypertension (HTN), type 2 diabetes mellitus (T2D), and obesity adversely affects health-related quality of life (HRQoL). Ambulatory circadian phenotypes (dipper/non-dipper/riser) and average real variability (ARV) may relate to mental well-being. We aimed to find whether ambulatory BP phenotypes and ARV are associated with the SF-36 mental component summary (MCS) in HTN+T2D+obesity.

**Materials and Methods:** In an observational cohort, 314 participants with HTN+T2D+obesity (mean age 58.9±9.7 years; 54% men), 262 had evaluable ambulatory blood pressure monitoring (ABPM) (dipper 34%, non-dipper 50%, riser 16%); completed the 36-Item Short-Form Health Survey (SF-36) and underwent 24-hour ambulatory BP monitoring (ABPM). The primary outcome was MCS. 24-h systolic ARV was computed from consecutive valid readings. Receiver-operating characteristic (ROC) analyses identified an ARV threshold for low MCS (the lowest quartile).

**Results:** Adjusted MCS showed a graded decrement across phenotypes: dipper 48.8 (95% CI 47.5–50.1), non-dipper 46.1 (45.1–47.2), riser 44.0 (42.5–45.6); $p<0.001$. ARV was independently and inversely associated with MCS; for low MCS, ARV discriminated better than SD and mean 24-h SBP (AUC 0.69 vs 0.63 and 0.58). The Youden-derived ARV cut-off ~12.5 mmHg yielded a sensitivity of 0.66 and specificity of 0.62. Simultaneous attainment of 24-h BP and HbA1c targets related to higher MCS (+3.1 points; $p<0.001$) and a greater high-MCS responder rate (52% vs 31%).

**Conclusion:** In HTN+T2D+obesity, abnormal circadian BP phenotypes and higher ARV identify patients with lower MCS beyond mean BP and may flag risk of low mental HRQoL and support integrated management toward dual control of 24-h BP and HbA1c.


**Keywords:** Blood pressure monitoring, hypertension, diabetes mellitus, obesity, quality of life, circadian rhythm.

## Introduction

Hypertension (HTN), type 2 diabetes (T2D), and obesity frequently co-occur and define a high-risk cardiometabolic phenotype encountered across primary and speciality care. While clinical management understandably prioritises "hard" outcomes (cardiovascular and renal events), patient-reported health-related quality of life (HRQoL) is a key determinant of adherence, self-management, and care utilisation. Generic instruments such as the 36-Item Short-Form Health Survey (SF-36) summarise eight domains into physical (PCS) and mental component scores (MCS), enabling cross-condition comparisons and clinically meaningful change thresholds. Recent work underscores that comorbidity burden—not simply the presence of T2D alone—drives HRQoL loss; for example, patients with T2D plus hypertension show lower SF-36 scores than those with T2D alone, with notable decrements in general health, whereas bodily pain was least affected.[1]

Determinants of HRQoL in T2D are multifactorial and include sociodemographic factors, adiposity, glycemic control, complications, and multimorbidity. In a multicenter study, higher BMI, longer diabetes duration, combined pharmacotherapy, and the presence of complications and comorbidities were each associated with lower PCS and/or MCS, highlighting targets for integrated management beyond glucose alone.[2]

Complementary evidence from primary care shows that systemic arterial hypertension nearly doubles the odds of poor SF-36 HRQoL among people with T2D, and that physical inactivity compounds risk—practical levers for routine care.[3]

Taken together, contemporary data position HRQoL as a clinically salient outcome in the multimorbid cardiometabolic phenotype.

Beyond static clinic blood pressure, ambulatory blood pressure monitoring (ABPM) provides circadian phenotypes (dipper/non-dipper/riser) and beat-to-beat/read-to-reading variability metrics such as average real variability (ARV). These features refine cardiovascular risk stratification; however, their relationship to patient-perceived well-being is understudied, particularly in individuals simultaneously living with HTN, T2D, and obesity. This gap is clinically important: non-dipping and "riser" profiles may reflect nocturnal sympathetic activation, sleep disruption, and autonomic dysregulation, all of which plausibly degrade energy, mood, and social functioning—domains central to the SF-36 MCS. Moreover, variability measures like ARV capture short-term hemodynamic lability that patients may experience as instability, palpitations, or fatigue—symptoms that can undermine daily participation and mental health. Yet few studies have examined whether these ABPM signatures add explanatory value for HRQoL beyond mean blood pressure and conventional metabolic covariates.

Parallel lines of evidence suggest that interventions which jointly improve metabolic control and hemodynamics can improve HRQoL. In severe obesity with T2D, 12-month outcomes after laparoscopic sleeve gastrectomy show significant gains in SF-36 PCS overall, with MCS improvements linked to remission and better metabolic indices—supporting the broader concept that integrated risk-factor control can translate into perceived well-being.[4]

Against this backdrop, routine assessment of HRQoL has been advocated as part of longitudinal diabetes care to inform tailored interventions.[1]

The primary study objective was to test whether circadian ABPM phenotypes (dipper/non-dipper/riser) and 24-h systolic BP ARV are independently associated with SF-36 MCS in patients with coexisting HTN, T2D, and obesity. Secondary objectives were to compare MCS across phenotypes and to assess whether "dual control" (24-h BP and HbA1c at target) is associated with higher MCS.

## Materials and Methods

*Study design and population*

We conducted an observational study of consecutive adults with established HTN and T2D followed in a cardiometabolic clinic.

Inclusion criteria: age ≥18 years; body mass index (BMI) ≥30 kg/m$^2$; established HTN and T2D; completion of the SF-36 questionnaire within ±2 weeks of ABPM; and availability of a valid 24-h ABPM recording within the previous 4 weeks.

Exclusion criteria: secondary hypertension; symptomatic heart failure, NYHA III–IV; recent acute coronary syndrome or stroke (<3 months); advanced CKD (stage 4–5; eGFR <30 mL/min/1.73 m$^2$); active inflammatory/autoimmune disease; pregnancy; or inability to complete questionnaires.

Rationale for key exclusions: We excluded NYHA III–IV heart failure and CKD stage 4–5 (eGFR <30) because advanced HF/CKD may markedly affect both ambulatory BP phenotypes/variability and HRQoL and could compromise ABPM feasibility/quality. Dose adjustments of routine therapies in patients with reduced eGFR (e.g., <60) were performed according to standard clinical practice and were not used as eligibility criteria. Current medications were recorded from medical records and participant reports at the study visit and grouped by drug class (RAS blockers, diuretics, calcium-channel blockers, beta-blockers, and antidepressant/anxiolytic/sedative drugs).

The protocol complied with the Declaration of Helsinki and was approved by the institutional bioethics committee (The Bioethics Committee of Kharkiv National Medical University, Kharkiv, Ukraine; protocol №3, 03.11.2021). All participants provided written informed consent before any study procedures.

*Ambulatory blood pressure monitoring and phenotypes*

ABPM was performed on a routine clinic day using a validated oscillometric device. Cuff size was selected per arm circumference. Measurements were scheduled every 20–30 minutes during daytime and every 30–60 minutes during nighttime; recordings with <70% valid readings, daytime <14 h or nighttime <6 h were repeated. Mean 24-h, daytime, and nighttime systolic/diastolic BP were computed using diary-defined sleep/wake periods (daytime = awake; nighttime = asleep), with manual editing when needed. Nocturnal SBP fall (%) was calculated as (daytime SBP − nighttime SBP) / daytime SBP ×100.

Circadian phenotypes were defined a priori as: dipper (10–20%), non-dipper (<10%), riser (≤0% dip), and extreme dipper (>20%). Twenty-four-hour BP variability was summarised by the ARV of SBP, computed as the mean of absolute differences between consecutive valid readings over 24 h; 24-h SD of SBP was also derived for sensitivity analyses.

The ARV of 24-h SBP was calculated according to the formula from Mena et al.[5] At the ABPM visit, we recorded age, sex, BMI, smoking status, diabetes duration, and clinic BP. Fasting blood samples within ±4 weeks provided HbA1c, lipid profile, creatinine (for eGFR using CKD-EPI), and high-sensitivity C-reactive protein (optional). Achievement of guideline targets was defined before analysis as 24-h BP control (<130/80 mmHg on the 24-h profile) and glycaemic control (HbA1c ≤7.0%); "dual control" indicated meeting both thresholds. Use of antidepressants/anxiolytics/sedatives was coded (yes/no).

*Health-related quality of life (SF-36)*

HRQoL was measured with the SF-36 (the validated Ukrainian SF-36 version with norm-based scoring (mean 50, SD 10), consistent across participants). Eight domain scores (0–100, higher is better) were computed per manual and aggregated into PCS and MCS component summary scores using standard algorithms, PCS reflects predominantly Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), and General Health (GH), whereas MCS reflects Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH) (standard SF-36 weighting approach). The primary outcome was MCS; secondary outcomes were VT, RE, SF, MH, and PCS. For cross-sectional risk stratification, we defined a high-MCS threshold as an MCS ≥3 points above the sample median; this label is used only to contrast groups at a single time point and does not imply individual change. In a longitudinal sensitivity analysis among participants who completed a repeat SF-36 at routine

follow-up, the minimal clinically important difference (MCID) was defined a priori as a ≥3-point within-person increase in MCS.

*Sample size and power*

This observational study used a consecutive sampling approach. A sensitivity analysis using G*Power (one-way ANOVA, three groups, α=0.05, power=0.80) indicated that the available ABPM sample (n=262) was sufficient for the primary comparison of MCS across circadian ABPM phenotypes, corresponding to a small-to-moderate between-group effect.

*Statistical analysis*

Continuous variables are presented as mean±SD or median (IQR), and categorical variables as counts (%). Between-group comparisons used t-tests/ANOVA or Mann–Whitney/Kruskal–Wallis as appropriate; proportions used $\chi^2$/Fisher tests. Associations of ABPM phenotypes and variability with HRQoL were examined using multivariable linear models with MCS (and domains) as dependent variables and the following prespecified covariates: age, sex, BMI, HbA1c, mean 24-h SBP, diabetes duration, smoking, antidepressant use, and lipid-lowering therapy. Diabetes duration was treated as a continuous covariate in all primary models and was not dichotomised (e.g., <10 vs ≥10 years) to avoid information loss and arbitrary cut-points. To estimate the ability of ARV to identify low MCS (the lowest quartile), we built logistic models and receiver-operating characteristic (ROC) curves; the optimal ARV cut-point was derived by Youden's index with 95% CIs. This Youden-derived threshold was then applied to define a binary high-ARV category for subsequent categorical analyses. We also modelled dual control (24-h BP + HbA1c targets) versus neither/one target using ANCOVA for mean differences in MCS and a binary MCID-responder analysis. Collinearity diagnostics and model assumptions (linearity, homoscedasticity, normality of residuals) were checked. Missing data were minimal; complete-case analysis was used. Two-sided $p<0.05$ was considered statistically significant. Analyses were performed in MedCalc, Belgium.

## Results

A total of 314 adults fulfilled eligibility and completed HRQoL assessment; of these, 262 (83.4%) also had evaluable 24-h ABPM recordings and comprised the ABPM analytic set (Table 1). The mean age was 58.9±9.7 years; 54% were men; median diabetes duration was 8.1 (IQR 4.0–14.0) years; and mean BMI was 33.6±4.7 kg/m$^2$. Antihypertensive therapy included a renin–angiotensin system blocker in 88%, a diuretic in 76%, a calcium-channel blocker in 69%, and a beta-blocker in 42%; 12% reported regular use of antidepressants,

anxiolytics, or sedatives. Among laboratory variables available within ±4 weeks, mean HbA1c was 7.4±1.1%, and mean eGFR 78±19 mL/min/1.73 $m^2$.

**Table 1.** Baseline characteristics of the study cohort

| Characteristic | Overall (n=314) | ABPM (n=262) | Dipper (n=89) | Non-dipper (n=131) | Riser (n=42) | p-value* |
|---|---|---|---|---|---|---|
| **Age, years** | 58.9 ± 9.7 | 58.9 ± 9.7 | 58.4 ± 9.8 | 59.1 ± 9.5 | 59.8 ± 9.9 | 0.183 |
| **Male sex, n (%)** | 170 (54.1) | 141 (53.8) | 47 (52.8) | 68 (51.9) | 26 (61.9) | 0.410 |
| **BMI, kg/$m^2$** | 33.6 ± 4.7 | 33.6 ± 4.7 | 33.3 ± 4.6 | 33.7 ± 4.7 | 34.0 ± 4.9 | 0.367 |
| **Diabetes duration, years** | 8.1 (4.0–14.0) | 8.1 (4.0–14.0) | 7.9 (4.0–13.5) | 8.2 (4.2–14.1) | 8.5 (4.1–14.8) | 0.521 |
| **HbA1c, %** | 7.4 ± 1.1 | 7.4 ± 1.1 | 7.3 ± 1.1 | 7.4 ± 1.2 | 7.6 ± 1.1 | 0.094 |
| **eGFR, mL/min/1.73 $m^2$** | 78 ± 19 | 78 ± 19 | 79 ± 18 | 78 ± 19 | 76 ± 20 | 0.441 |
| **Antidepressants/anxiolytics/ sedatives, n (%)** | 38 (12.1) | 31 (11.8) | 8 (9.0) | 15 (11.5) | 8 (19.0) | 0.218 |
| **24-h mean SBP / DBP, mmHg** | --- | 132 ± 12 / 78 ± 8 | 130 ± 11 / 77 ± 7 | 132 ± 12 / 78 ± 8 | 136 ± 14 / 79 ± 9 | 0.020 / 0.211 |
| **Daytime SBP / DBP, mmHg** | --- | 136 ± 13 / 81 ± 8 | --- | --- | --- | --- |
| **Nighttime SBP / DBP, mmHg** | --- | 124 ± 14 / 73 ± 9 | --- | --- | --- | --- |
| **ARV 24-h SBP, mmHg** | --- | 11.6 ± 3.2 | 10.4 ± 2.7 | 11.7 ± 3.0 | 13.5 ± 3.4 | 0.001 |
| **SD 24-h SBP, mmHg** | --- | 12.9 ± 3.8 | 12.2 ± 3.5 | 13.0 ± 3.7 | 13.9 ± 4.1 | 0.030 |
| **Phenotype distribution, n (%)** | --- | --- | 89 (34.0) | 131 (50.0) | 42 (16.0) | --- |
| **24-h BP control <130/80, n (%)** | --- | 120 (46) | 44 (49.4) | 57 (43.5) | 19 (45.2) | 0.581 |
| **HbA1c ≤7.0%, n (%)** | 154 (49.0) | 129 (48) | 46 (51.7) | 62 (47.3) | 21 (50.0) | 0.788 |
| **Dual control (both), n (%)** | --- | 89 (34.0) | 34 (38.2) | 40 (30.5) | 15 (35.7) | 0.420 |

BMI, body mass index; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARV, average real variability; SD, standard deviation; ABPM, ambulatory blood pressure monitoring; BP, blood pressure. Data are presented as mean ± standard deviation or number (percentage), as appropriate. Dipper, non-dipper, and riser refer to nocturnal blood pressure patterns based on ABPM measurements. *Significant relationship, p<0.05

Across the ABPM cohort, the 24-h mean systolic/diastolic BP was 132±12 / 78±8 mmHg; daytime 136±13/81±8 mmHg; nighttime 124±14/73±9 mmHg. The distribution of circadian phenotypes was: dipper 34% (n=89), non-dipper 50% (n=131), and riser 16% (n=42); over dippers were not observed. The 24-h ARV of SBP averaged 11.6±3.2 mmHg (range 6.2–20.7), while the 24-h SD of SBP was 12.9±3.8 mmHg. By prespecified clinical thresholds, 24-h BP control (<130/80 mmHg) was achieved in 46%, HbA1c ≤7.0% in 48%, and dual control (both targets) in 34% of participants. In the full HRQoL cohort (n=314), the MCS was 46.9±9.1 and the PCS 46.2±8.7 (norm-based scoring). Among those with ABPM (n=262), adjusted comparisons across circadian phenotypes demonstrated a graded decrement in MCS from dipper to riser (Table 2): 48.8 (95% CI 47.5–50.1) in dippers, 46.1 (45.1–47.2) in non-dippers, and 44.0 (42.5–45.6) in risers (p=0.001). VT, SF, and MH exhibited parallel gradients (all p<0.01), whereas PCS differences were modest and non-significant after adjustment. Domain-level adjusted means are shown in Table 2.

**Table 2.** SF-36 outcomes by ABPM phenotype (adjusted estimates*)

| Outcome | Dipper (n=89) | Non-dipper (n=131) | Riser (n=42) | P** |
|---|---|---|---|---|
| **MCS (adjusted mean, 95% CI)** | 48.8 (47.5–50.1) | 46.1 (45.1–47.2) | 44.0 (42.5–45.6) | 0.001 |
| VT (adjusted mean) | 62 | 56 | 52 | 0.003 |
| SF (adjusted mean) | 79 | 73 | 69 | 0.007 |
| MH (adjusted mean) | 75 | 70 | 66 | 0.001 |

ABPM: Ambulatory blood pressure monitoring, MCS: Mental Component Summary; VT: vitality; SF: social functioning; MH: mental health; CI: confidence interval. *Adjusted for age, sex, BMI, HbA1c, mean 24-h SBP, diabetes duration, smoking, antidepressant/anxiolytic/sedative use, and lipid-lowering therapy **Significant relationship, $p < 0.05$

Associations between ABPM features and HRQoL showed that in multivariable linear models (covariates: age, sex, BMI, HbA1c, mean 24-h SBP, diabetes duration, smoking, antidepressant use, lipid-lowering therapy), non-dipper and riser phenotypes were independently associated with lower MCS compared with dipper (overall p<0.001, Table 2). The estimated adjusted mean differences vs dipper were −2.7 points (95% CI −3.8 to −1.2) for non-dippers and −4.8 (−6.7 to −2.9) for risers. Patterns were consistent for VT, SF, and MH (all p<0.01), with smaller and non-significant effects for PCS.

Categorising ARV into tertiles yielded a stepwise risk: compared with T1 (≤9.8 mmHg), T2 (9.9–12.4 mmHg) had aOR 1.42 (95% CI 0.88–2.28; p=0.15), and T3 (≥12.5 mmHg) had aOR 2.12 (1.28–3.52; p=0.003) (Table 3). In multivariable logistic models defining low MCS as the cohort-specific lowest quartile (≤42 points), each 1-

mmHg increase in 24-h SBP ARV was associated with higher odds of low MCS (aOR 1.23; 95% CI 1.08–1.40; p=0.002), independent of mean 24-h SBP and metabolic covariates (Table 3).

Receiver-operating characteristic (ROC) analyses showed that ARV outperformed SD and mean 24-h SBP for identifying low MCS. The area under the curve (AUC) for ARV was 0.69 (95% CI 0.63–0.75), compared with 0.63 (0.57–0.70) for SD and 0.58 (0.52–0.64) for mean 24-h SBP. The Youden-derived ARV threshold was ~12.5 mmHg, yielding a sensitivity of 0.66 and a specificity of 0.62 for low MCS. Performance was similar across sex and BMI strata (interaction p>0.10).

Dual target attainment and clinically meaningful change. In analyses comparing participants with dual control (24-h BP and HbA1c at target) versus those with neither or only one target achieved, adjusted mean MCS was higher by +3.1 points (95% CI +1.5 to +4.6; p<0.001). In a cross-sectional responder framework (high-MCS threshold: MCS ≥3 points above the sample median), the responder rate was 52% with dual control versus 31% otherwise (risk ratio 1.68; 95% CI 1.28–2.19; p<0.001).

Results were robust in sensitivity analyses: excluding participants on antidepressants/anxiolytics/sedatives (n=31) produced nearly identical estimates for phenotype and ARV associations with MCS (all p values within 0.02 of primary). Using fixed clock-time windows for day/night in place of diary-based sleep intervals yielded similar phenotype classification and effect sizes. Additional adjustment for the number of antihypertensive classes and for statin use did not materially alter coefficients. When defining low MCS as the lowest tertile rather than quartile, the ARV AUC was 0.68 (0.62–0.74) and the optimal threshold remained close to 12.5 mmHg. Substituting 24-h SD for ARV attenuated associations and discrimination, consistent with the primary analysis.

There were no adverse events related to ABPM acquisition. Missingness was low (<3% for any single covariate); complete-case analyses were used for models and ROC. The proportion of invalid ABPM recordings on the first attempt was 6.8%; these were repeated per protocol and excluded if repeat quality criteria were not met (final evaluable n=262).

**Table 3.** ARV and dual control in relation to low MCS (adjusted models*)

| Metric | Categories / Predictor | Estimate | 95% CI | p |
|---|---|---|---|---|
| **Low MCS (lowest quartile)** | **ARV T2 vs T1** | aOR 1.42 | 0.88–2.28 | 0.150 |
| | **ARV T3 vs T1** | aOR 2.12 | 1.28–3.52 | 0.003 |
| **ROC AUC (low MCS)** | **ARV (mmHg)** | 0.69 | 0.63–0.75 | # |
| | 24-h SD SBP (mmHg) | 0.63 | 0.57–0.70 | --- |
| | Mean 24-h SBP (mmHg) | 0.58 | 0.52–0.64 | --- |
| **Dual control (24-h BP+HbA1c at target)** | ΔMCS (adjusted mean) | +3.1 | +1.5 to +4.6 | 0.001 |
| | High-MCS responders | RR 1.68 | 1.28–2.19 | 0.001 |

MCS: Mental Component Summary; ARV: average real variability; T1–T3: tertiles 1 to 3; aOR: adjusted odds ratio; ROC: receiver operating characteristic; AUC: area under the curve; SD: standard deviation; SBP: systolic blood pressure; BP: blood pressure; HbA1c: glycated hemoglobin; ΔMCS: change in Mental Component Summary score; RR: relative risk; CI: confidence interval. *Models adjusted for age, sex, BMI, HbA1c, mean 24-h SBP, diabetes duration, smoking, antidepressant/anxiolytic/sedative use, and lipid-lowering therapy, as applicable (see Statistical analysis) # – Youden-derived ARV threshold ≈12.5 mmHg; sensitivity 0.66; specificity 0.62

## Discussion

This study highlights three clinically actionable messages for managing the multimorbidity phenotype of HTN plus T2D and obesity. The riser phenotype—i.e., absent nocturnal BP fall—was consistently associated with the lowest MCS and the largest drops in VT/SF/MH; non-dippers showed intermediate impairment, while dippers had the most favourable profile.

Circadian BP phenotypes (dipper/non-dipper/riser) and ARV are independently associated with the mental component of health-related quality of life (HRQoL) and with emotion/energy domains (vitality, social functioning, mental health), beyond mean BP and conventional cardiometabolic covariates. Second, an ARV threshold around ~12.5 mmHg pragmatically flags patients at higher risk of low MCS. Third, simultaneous attainment of 24-h BP and HbA1c targets is associated with clinically meaningful (MCID-level) gains in MCS, suggesting that integrated hemodynamic and glycemic control shifts perceived well-being, not only "hard" outcomes.

Interpretation and putative mechanisms. Non-dipping and riser patterns indicate loss of the normal nocturnal BP decline and often reflect autonomic dysregulation, heightened nighttime sympathetic tone, impaired baroreflex control, obstructive sleep apnea, or increased arterial stiffness. Contemporary work underscores that abnormal circadian BP rhythms track with neurocognitive risk and sleep disruption, supporting a pathway whereby nocturnal sympathetic activation and fragmented sleep erode mental health and vitality. [6] ARV captures short-term, successive BP fluctuations across the 24-h cycle; greater lability may be intrinsically "fatiguing," perceived as inner tension, palpitations, non-restorative sleep, and daytime tiredness, which plausibly depresses SF-36 VT/SF/MH and overall MCS.

The observed association between dual target attainment (24-h BP + HbA1c) and better MCS is biologically consistent. Glycemic improvement can lessen nocturia and neuropathic discomfort, improve sleep continuity, and reduce low-grade inflammation; when combined with smoother 24-h hemodynamics, this may reduce somatic arousal and fatigue—key drivers of the mental domains. Recent primary-care and speciality studies show that in multimorbid T2D populations, non-biomedical determinants (pain, inactivity, adherence, social and economic stressors) materially shape HRQoL alongside clinical parameters.[7,8] Our findings fit this multidimensional picture while adding an ambulatory hemodynamic lens (phenotype + variability).

Hypertension and HRQoL. A multi-facility cross-sectional study analysis using WHOQOL-BREF confirmed lower HRQoL among adults with HTN and identified modifiable correlates (physical inactivity, low social support, comorbidity, longer antihypertensive treatment duration) as key levers.[9] These data align with our emphasis on targeted behavioural and system-level supports once high-risk ABPM profiles are identified.

A recent global meta-analysis of 22 studies (n=5,447) confirmed a consistent HRQoL decrement in hypertension on the SF-36—pooled means PCS 60.0 and MCS 60.1, falling after trim-and-fill to 52.3% (PCS) and 46.4% (MCS), with substantial heterogeneity by continent, data-collection mode, and sample size.[10] In our cohort, MCS 46.9 ± 9.1 closely matches the bias-adjusted global MCS, reinforcing the salience of mental HRQoL impairment in treated hypertension. We also demonstrate a graded, confounder-adjusted decline across ambulatory phenotypes (dipper – non-dipper – riser), underscoring circadian BP dysregulation as a determinant of mental well-being. Beyond the meta-analytic scope, non-dipping/riser status and higher 24-h ARV independently track lower MCS and VT/SF/MH and outperform SD and mean 24-h SBP for discriminating low MCS. Despite high between-study heterogeneity, the concordance between our MCS and the bias-adjusted benchmark strengthens the external relevance of our results to European outpatient care.

In a Croatian T2D cohort, Kolarić et al. used WHOQOL-BREF and showed that HRQoL declined across all domains, with the lowest scores in patients with multiple chronic complications and the highest in those without complications.[11] In this study, domain-specific patterns emerged—social functioning was poorest with

retinopathy/neuropathy, while physical functioning was lowest with nephropathy or diabetic foot ulcer—highlighting the cumulative burden of vascular and neuropathic damage. Our multimorbid cohort complements these findings by demonstrating that, beyond structural complication load, circadian BP phenotypes and higher 24-h ARV independently track lower MCS on the SF-36. Notably, our mean MCS sits below the psychological/social WHOQOL-BREF means reported by Kolarić et al., plausibly reflecting instrument scaling, greater clinical complexity, and the added impact of circadian BP dysregulation. Together, these data argue for an integrated approach that screens for diabetes complications while routinely performing ABPM to detect high-variability, non-dipping/rising patterns, thereby targeting patients most likely to benefit from combined cardio-metabolic optimisation and psychosocial support.[11]

Alsaidan et al. surveyed T2D in Saudi primary care using the SF-20 (Arabic) and found HRQoL highest for role functioning but lowest for social functioning and pain, with higher odds of better HRQoL in men and those on oral hypoglycemics, and lower in obese, irregular-follow-up, or comorbid patients.[8] In our HTN+T2D+obesity cohort, mental health–related domains (MCS and VT/SF/MH) are likewise most impaired, and we further show that ABPM phenotypes BP and higher 24-h ARV independently track poorer MCS beyond mean BP and metabolic covariates. Despite different instruments (SF-20 vs SF-36), both studies converge on actionable levers—reinforcing follow-up/adherence and pain management—while our data adds circadian BP dysregulation as a modifiable correlate.

In a Romanian T2D cohort with inadequate glycemic control, age and BMI were inversely associated with diabetes-specific QoL (ADDQoL), while SF-36 domains showed minimal associations and no link with HbA1c.[7] Echoing this, our data suggest that mental HRQoL is driven less by glycemia per se and more by hemodynamic features—non-dipping/riser status and higher 24-h ARV—independent of age and BMI. In a cross-sectional study in Mexico, 80% of patients had SF-36 > 50, but physical inactivity (OR 2.76), hypertension (OR 1.93), and female gender (OR 2.82) independently increased the odds of low HRQoL (SF-36 ≤ 50). A higher percentage of body fat was associated with lower SF-36 total and domain scores (especially for physical function, vitality, and mental health), while no association was found with HbA1c.[3] A 2025 public-health study showed graded HRQoL loss from T2D alone to T2D with comorbidities, with the largest decrement in T2D+ cancer, followed by thyroid disease, while hypertension and kidney disease were associated with modest reductions.[1] Together, these reinforce that co-occurring HTN meaningfully worsens the HRQoL profile in T2D—consistent with our observation that non-dipping/riser and higher ARV map most strongly to mental/energy domains.

Among Indonesian adults with hypertension, counselling-intensive care was associated with greater gains in EQ-5D-5L utility over 3 months versus usual care; moreover, patients attending blood-pressure checks twice monthly had higher utility values than those attending monthly (0.85 vs 0.74), suggesting that structured counselling and more frequent monitoring can translate into measurable HRQoL benefits.[12] In T2D, 3 months'

use of a digital self-management program improved RAND-36 role-physical, role-emotional and emotional well-being, but no between-group differences were seen in other domains, and effects were not sustained at 6 months.[13] Structured counselling and self-management interventions have been associated with improvements in patient-reported outcomes in cardiometabolic settings. [12,13] These findings support our practical suggestion to triage patients with ARV ≥ ~12.5 mmHg or non-dipping/riser into brief, protocolized psycho-behavioural support (education, graded activity, sleep hygiene, medication-taking support, family involvement).

In Afghanistan, more than half of adults receiving care for hypertension screened positive for depressive symptoms, and depression was independently associated with poor blood-pressure control, along with low education, low income, physical inactivity, and comorbidity.[14] Complementing this, in Afghan adults with T2D, hypertension was common (~55%), and depressive symptoms were associated with ≈3-fold higher odds of coexisting hypertension, reinforcing the tight coupling between mood disturbance and BP dysregulation.[15]

These data reinforce the bidirectional linkage between mood and hemodynamic control and help explain why patients with greater ambulatory BP instability often report worse mental HRQoL. This triangulates with our finding that circadian BP type sits close to MCS.

Abnormal BP rhythms and variability are established predictors of adverse “hard” outcomes; showing that these same ambulatory signatures align with the mental domains of HRQoL strengthens the case for routine ABPM not only to refine cardiovascular risk but also to surface hidden psychosocial burden that standard clinic BP may miss.[6]

In a comparative study of hypertensive outpatients (WHOQOL-BREF), costs of care (direct/indirect/total) inversely tracked HRQoL, and multivariable models highlighted income, complication burden, physical activity, smoking, and urban residence as key correlates—underscoring the need for cost-mitigation and integrated behavioural support in hypertension care.[16]

Complementing our results, Guidotti et al.[17] found in hypertensive outpatients that lower SF-36 Vitality was associated with greater psychological distress (SCL-90-R GSI), with Social Functioning partially mediating this link. This dovetails with our observation that VT, SF, and MCS cluster with ambulatory BP instability, reinforcing the case for interventions that boost energy and structured social engagement—particularly in non-dippers/risers. Practically, routine screening for low VT and impaired SF can flag patients most likely to benefit from integrated psycho-behavioural support alongside phenotype-guided BP therapy.

Measure HRQoL routinely. For HTN + T2D + obesity, capture SF-36 (or SF-12) at baseline and follow-up; track MCS and the VT/SF/MH triad specifically, as these are sensitive to pain, inactivity, adherence and social

constraints.[7,8] ABPM yields circadian status (dipper/non-dipper/riser) and ARV—both informative for organ-risk and mental HRQoL risk. Adopt a simple ARV alert. Treat ARV ≥ ~12.5 mmHg as a pragmatic flag for a likely mental-energy burden, triggering a short, structured psychosocial package (tailored education, activity nudges, sleep hygiene, pain management, family engagement) and screening for OSA where appropriate. Aim for dual targets. Manage to both 24-h BP and HbA1c targets, with regular feedback. Our data suggest that dual control is associated with MCID-sized improvements in MCS. Digital self-management and structured exercise programs can help sustain gains.[13] Tailor therapy by ABPM phenotype. In non-dippers/risers, consider chronotherapy, optimise long-acting combinations, and systematically evaluate for OSA; monitor pain and sleep, which strongly influence VT/SF/MH. Address social determinants. Costs, activity habits, and complication load explain a substantial share of HRQoL variance in HTN; integrating social and behavioural support is therefore not optional.[14] In practice, riser or non-dipper status and/or ARV ≥12.5 mmHg should prompt OSA screening, review of 24-h antihypertensive coverage (long-acting combinations, possible evening dosing/chronotherapy), and brief psycho-behavioural support, while pursuing dual control of 24-h BP and HbA1c.

Limitations. Key strengths of the study include using ARV to capture short-term 24-h variability beyond mean BP; multivariable analyses adjusting for metabolic and treatment covariates; and an MCID-anchored responder analysis for MCS, which improves clinical interpretability. Limitations include an observational, single-centre design (precluding causal inference and potentially limiting generalizability) and the absence of dedicated anxiety/depression scales—we used SF-36 VT/SF/MH as validated proxies. Even though multiple recent studies consistently document the adverse impact of HTN and comorbidity burden on HRQoL,[1, 11, 16] these findings warrant confirmation in larger, multicenter cohorts. Finally, we did not model response shift—changes in internal standards or valuation of health states over time—which can bias apparent change in HRQoL; hypertension studies suggest this phenomenon can differentially affect physical vs mental components and warrants attention in longitudinal designs.[7, 10]

We did not prespecify a universal ARV cut-off; the 12.5 mmHg value was cohort-derived for low MCS discrimination and may vary across settings, underscoring the need for further multicenter studies to validate the generalizability of these findings.

Conclusions and perspectives. Test whether lowering ARV through combined strategies—chronotherapy and long-acting regimens for smoother 24-h coverage plus non-pharmacologic autonomic “quieting” (structured exercise, sleep optimisation, pain management, weight loss, digital maintenance)—yields incremental MCS benefits beyond those from mean BP reduction alone. Evidence that task-oriented nursing and exercise programs improve HRQoL in cardiovascular populations makes this testable.[18] Second, evaluate antihypertensive chronotherapy in non-dippers/risers with HRQoL endpoints, integrating OSA work-up. Third,

embed low-intensity maintenance contacts (nurse- or app-delivered), because without maintenance, behavioural effects often wane by 3–6 months; recent trials show that structured follow-up sustains SF-36 gains.[13,18] In parallel, bibliometric mapping indicates accelerating interest in T2D HRQoL measurement and psychosocial correlates, but few studies integrate ambulatory hemodynamic phenotyping—an opportunity our work begins to address.[1]

In adults with hypertension, type 2 diabetes, and obesity, non-dipper/riser circadian phenotypes and greater 24-h BP ARV were independently associated with lower SF-36 MCS, whereas simultaneous attainment of 24-h BP and HbA1c targets was associated with higher MCS. ARV can support risk stratification and triage to integrated care (chronotherapy, long-acting combinations, screening for obstructive sleep apnea, and behavioural support). Prospective studies are warranted to test whether reducing ARV and correcting circadian BP abnormalities improve MCS.

**Ethical Considerations:** Approval was received from the Ethics Committee of Kharkiv National Medical University, Kharkiv, Ukraine (Protocol No 3, 03.11.2021), and the Principles of the Helsinki Declaration were followed.

**Conflict of Interest:** The authors declare no conflict of interest.

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# ASSESSMENT OF THE RELATIONSHIP BETWEEN GASTROESOPHAGEAL REFLUX DISEASE AND SLEEP QUALITY IN PHYSICIANS

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## Abstract

**Objectives:** Gastroesophageal reflux disease (GERD) is a common gastrointestinal condition that can impair quality of life and lead to complications. Research assistant physicians are especially at risk due to factors such as long working hours, high workload, irregular eating habits, and stress. This study aimed to assess the prevalence of GERD and its relationship with sleep quality among research assistant physicians.

**Materials and Methods:** This cross-sectional study included 446 research assistant physicians working at Selçuk University Faculty of Medicine Hospital between 2024 and 2025. Data were collected using a sociodemographic questionnaire, the Reflux Disease Questionnaire (RDQ), the Pittsburgh Sleep Quality Index (PSQI), and body composition analysis via bioelectrical impedance (BIA). Only participants meeting the inclusion criteria and providing informed consent were included. Ethical approval was obtained.

**Results:** The mean age was 28.82 years, with 43.9% male participants. GERD prevalence was found to be 42.6%. GERD was significantly associated with marital status, consumption of fatty and spicy foods, obesity, visceral fat, and poor sleep quality ($p<0.05$). Poor sleep quality was also linked to nighttime eating, light exposure at night, obesity, and shift work. Participants with GERD had significantly worse sleep quality ($p<0.001$).

**Conclusion:** GERD and poor sleep quality are prevalent among research assistant physicians and are influenced by occupational and lifestyle factors. Preventive measures, early diagnosis, and improvements in working conditions and sleep hygiene should be emphasised in health policy planning.

**Keywords:** Gastroesophageal reflux disease, physicians, sleep quality, prevalence, visceral fat, lifestyle habits.

## Introduction

Gastroesophageal reflux disease (GERD) is a chronic disorder frequently observed in industrialised societies and represents one of the leading causes of visits to primary care services. The hallmark symptoms of GERD include pyrosis, regurgitation, globus sensation, dysphagia, and retrosternal pain. If inadequately managed, these symptoms can lead to significant clinical complications, including an elevated risk of malignancies, particularly oesophageal adenocarcinoma.[1]

The pathogenesis of GERD is multifactorial, primarily involving transient relaxations and pressure abnormalities of the lower oesophageal sphincter (LES). Dietary factors such as high-fat foods and chocolate, alcohol consumption, smoking, and certain medications can reduce LES pressure and increase reflux.[2] Risk factors identified over time include age over 50, low socioeconomic status, tobacco use, excessive alcohol intake, connective tissue disorders, pregnancy, postprandial supine position, and anticholinergic medication use. Anatomical changes like hiatal hernia and increased intra-abdominal pressure, commonly seen in obese individuals, further increase the risk of GERD.[2]

Epidemiological data reveal that GERD is a prevalent health issue in Western populations, whereas its prevalence is relatively low in Eastern regions such as Asia and Africa.[4] Globally, the prevalence of GERD ranges from 2.5% to 33.1%, with a reported rate of 22.8% in Turkey as of 2017.[3,4]

Accurate diagnosis of GERD begins with a thorough clinical history emphasising symptom characterisation, including duration, severity, and relation to dietary intake, posture, and physical activity, as well as assessment of quality-of-life impact. In patients presenting with classic symptoms such as heartburn and regurgitation, presumptive diagnosis is often sufficient and can be supported by a proton pump inhibitor (PPI) trial. However, in patients who present with atypical or alarming symptoms, diagnostic investigations are recommended before empirical therapy.[2] The management of mild-to-moderate GERD typically involves lifestyle modifications and PPI therapy, with additional pharmacological or surgical interventions reserved for refractory or severe cases.[2]

GERD affects approximately 13.0% of the adult population worldwide at least once weekly, with up to 25.0% of patients experiencing sleep disturbances related to nocturnal reflux.[5] The interplay between sleep and GERD is an active area of research. Physiological changes during sleep—such as diminished oesophageal peristalsis, reduced saliva production, decreased swallowing frequency, and the supine position—contribute to prolonged oesophageal acid exposure and exacerbate GERD symptoms. Moreover, protective reflexes that limit gastric content reflux diminish, particularly during deep (N3) sleep.[6]

GERD disrupts sleep architecture by inducing frequent nocturnal awakenings and arousals. Conversely, sleep deprivation may exacerbate GERD by increasing oesophageal acid sensitivity, creating a vicious cycle in which GERD and poor sleep quality mutually reinforce each other.[7] Emerging evidence suggests a bidirectional relationship between sleep disturbances and functional gastrointestinal disorders, with sleep quality independently predicting GERD symptom severity.[8]

Given the limited data on GERD incidence and its association with sleep quality among healthcare professionals, this study aims to evaluate these parameters in research assistant physicians exposed to chronic occupational risk factors.

## Materials and Methods

*Study participants*

This study was conducted among research assistant physicians between 2024 and 2025. It was carried out in accordance with the 1964 Helsinki Declaration and its subsequent updates.

*Study population*

The current study was conducted on a total of 446 physicians, accounting for 80% of the 554 research physician participants. The participants were classified as internal medicine (n=265; 80.0%), surgical medicine (n=160; 80.0%), or basic medicine (n=21; 80.7%). Participation was voluntary. Pregnant women, those with obstructive sleep apnea syndrome (OSAS), those with a diagnosis of major depression, those with a diagnosis of Gastrointestinal System (GIS) malignancy, those who had undergone GIS surgery, and those using psychiatric medication were excluded from the study.

*Survey and Measurements*

Data were collected through a face–to–face survey consisting of four sections. The questionnaire included a sociodemographic information form (21 questions), the Reflux Disease Questionnaire (RDQ) for GERD assessment, and the Pittsburgh Sleep Quality Index (PSQI) for sleep quality. Body anthropometric measurements were performed via InBody bioelectrical impedance analysis (BIA).

Sociodemographic Information Form: This form included 21 questions regarding age, sex, marital status, number of people living in the same household, field of expertise, work schedule, tobacco and alcohol use, physical activity, chronic diseases, regular medication use, caffeine consumption, sleep habits, and the consumption of foods that increase the risk of GERD.

*Reflux Disease Questionnaire (RDQ):*

The RDQ was developed by Shaw et al. in 2001, and its Turkish validity and reliability study was conducted by Hançerlioğlu et al. in 2021.[9,10.] It is a 12-item self-reported scale assessing upper gastrointestinal symptoms over the past week. Half of the items evaluate symptom frequency, and the other half assess symptom severity. The scale includes three subscales: regurgitation, retrosternal pain, and dyspepsia. Each item is scored from 0 (none) to 5 (very severe/very frequent), with a total score ranging from 0 to 60. A total score of ≥12 indicates the presence of GERD. The scale has high internal consistency (Cronbach's alpha = 0.85).[9]

*Pittsburgh Sleep Quality Index (PSQI):*

The PSQI was developed by Buysse et al. in 1989, and its Turkish validity and reliability study was conducted by Ağargün et al. in 1996.[11,12] It is a self-reported scale consisting of 19 items that assesses sleep quality over the past month. The PSQI includes seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored between 0 and 3, with a total score ranging from 0 to 21. A total score above 5 indicates poor sleep quality. The internal consistency of the scale is good, with a Cronbach's alpha coefficient of 0.80.[12]

*Body composition analysis:*

Anthropometric measurements and body composition measurements were performed using an InBody 770 bioelectrical impedance analysis device. The measured parameters included height (using the Seca 264 stadiometer), weight, BMI, fat mass, fat-free body mass, body fat percentage (BFP), visceral fat area (VFA), and waist-to-hip ratio. BMI was classified according to the World Health Organisation (WHO) criteria. A VVA ≥100 $cm^2$ was considered high visceral fat.[13]

*Ethical Approval and Informed Consent*

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1964) and its later amendments. Ethical approval was obtained from the Selcuk University Faculty of Medicine Ethics Committee (Decision No: 2024/366, dated July 16, 2024). Written informed consent was obtained from all participants before their enrollment. Clinical trial registration: Not applicable

*Statistical analysis*

All the data were analysed via the IBM SPSS 25.0 statistical software package. Before analysis, data normality was assessed via the Shapiro–Wilk normality test and Q–Q plots; group variance homogeneity was checked via

Levene's homogeneity test. Numerical variables in the study are presented as the means ± standard deviations, and categorical variables are presented as frequencies (n) and percentages. Sociodemographic, medical, and professional characteristics of physicians with and without GERD and those with poor and good sleep quality were compared via Pearson's chi-square test, Yates-corrected chi-square test, or Fisher–Freeman–Halton test. A p-value of <0.05 was considered to indicate statistical significance. Factors influencing the presence of GERD and sleep quality among physicians were identified via binary logistic regression analysis. Odds ratios are reported with 95.0% confidence intervals.

## Results

A total of 446 physicians were included in the study. Among the participants, 43.9% were male, and 56.1% were female, with a mean age of 28.82 years. Of the physicians, 44.8% were single, and 55.2% were married. Regarding their living arrangements, 25.6% lived alone, 16.8% with their parents, 33.4% with their spouses, 21.7% with their spouses and children, and 2.5% with others. In terms of physical activity, 40.6% did not engage in any, 45.3% exercised 1–2 times per week, and 14.1% exercised ≥3 times per week. Consumption of tomato paste and spicy foods was reported as follows: 1.8% once a month, 16.8% 1–2 times per week, 45.5% 3–5 times per week, and 35.9% daily. According to BMI distribution, 3.8% of the physicians were underweight, 49.3% were of normal weight, 33.2% were overweight, and 13.7% were obese. The sociodemographic characteristics are summarised in Table 1.

The frequency of married physicians was significantly higher in the GERD group (frequency: 63.7%) compared to those living alone (p=0.002). The frequency of physicians engaging in physical activity three or more times per week was significantly lower in the GERD group (frequency: 7.9%) (p=0.004). Daily consumption frequency of tomato paste and spicy foods was higher among physicians with GERD (frequency: 46.8%) than those without (frequency: 27.7%) (p<0.001). Eating within two hours before bedtime (frequency: 41.6% vs. 32.4%; p=0.011) and consuming three or more cups of tea/coffee per day (frequency: 63.7% vs. lower; p<0.001) were also significantly more frequent in the GERD group. Obesity (frequency: 25.3%) and high visceral fat levels (frequency: 59.5%) were significantly more prevalent in physicians with GERD (p<0.001). No significant differences were found between groups regarding sex, smoking, alcohol use, chronic disease presence, or regular medication use (p>0.05). There was no association between department or work schedule and GERD prevalence (p>0.05). The prevalence of poor sleep quality was significantly higher in the GERD group (frequency: 76.8%) compared to those without GERD (frequency: 40.2%) (p<0.001) (Table 2).

**Table 1.** Lifestyle habits of the physicians

| Feature | n | (%) |
|---|---|---|
| **Food Before Sleep** | | |
| No | 121 | (27.2%) |
| Sometimes | 163 | (36.5%) |
| Yes | 162 | (36.3%) |
| **Tea-Coffee Consumption** | | |
| No tea-coffee intake | 8 | (1.8%) |
| 1-2 cups a day | 200 | (44.8%) |
| ≥3 cups per day | 238 | (53.4%) |
| **Use of a night light** | | |
| No | 413 | (92.6%) |
| Yes | 33 | (7.4%) |
| **Blackout Curtain Usage** | | |
| No | 245 | (54.9%) |
| Yes | 201 | (45.1%) |
| **Using the Phone Before Going to Sleep** | | |
| No | 52 | (11.7%) |
| Yes | 394 | (88.3%) |
| **Visceral Fat** | | |
| Normal | 253 | (56.7%) |
| High (≥100cm$^2$) | 193 | (43.3%) |
| **Cigarette Use** | | |
| Never smokers | 278 | (62.3%) |
| Former smokers | 18 | (4.0%) |
| Occasionally | 60 | (13.5%) |
| Current smokers | 90 | (20.2%) |
| **Alcohol Use** | | |
| Non drinker | 379 | (85.0%) |
| Occasionally | 52 | (11.7%) |
| User | 15 | (3.3%) |
| **Presence of Chronic Disease** | | |
| None | 406 | (91.0%) |
| Yes | 40 | (9.0%) |
| **Drugs** | | |
| No drugs | 425 | (95.3%) |
| Yes | 21 | (4.7%) |
| **Total** | 446 | (100.0%) |

**Table 2.** Associations between sociodemographic, health status and occupational characteristics of physicians and the frequency of gastroesophageal reflux disease

| Variable | GERD Present (n=190) | No GERD (n=256) | *p* |
|---|---|---|---|
| **Gender** | n (%) | n (%) | 0.923[1] |
| Male | 83 (43.7%) | 113 (44.1%) | |
| Woman | 107 (56.3%) | 143 (55.9%) | |
| **Marital Status** | n (%) | n (%) | 0.002[1] |
| Single | 69 (36.3%) | 131 (51.2%) | |
| Married | 121 (63.7%) | 125 (48.8%) | |
| **Person Living in** | n (%) | n (%) | 0.007[1] |
| Alone | 35 (18.4%) | 79 (30.9%) | |
| Parents | 31 (16.3%) | 44 (17.2%) | |
| Spouse | 74 (38.9%) | 75 (29.3%) | |
| Spouse-child | 48 (25.3%) | 49 (19.1%) | |
| Other* | 2 (1.1%) | 9 (3.5%) | |
| **Physical Activity** | n (%) | n (%) | 0.004[2] |
| No | 85 (44.7%) | 96 (37.5%) | |
| 1-2 times a week | 90 (47.4%) | 112 (43.8%) | |
| ≥3 times per week | 15 (7.9%) | 48 (18.8%) | |
| **Spicy Sauce Consumption** | n (%) | n (%) | <0.001[2] |
| Once a month or never | 0 (0.0%) | 8 (3.1%) | |
| 1-2 times a week | 20 (10.5%) | 55 (21.5%) | |
| 3-5 times a week | 81 (42.6%) | 122 (47.7%) | |
| Every day | 89 (46.8%) | 71 (27.7%) | |
| **Food Before Sleep** | n (%) | n (%) | 0.011[1] |
| No | 38 (20%) | 83 (32.4%) | |
| Sometimes | 73 (38.4%) | 90 (35.2%) | |
| Yes | 79 (41.6%) | 83 (32.4%) | |
| **Tea-Coffee Consumption** | n (%) | n (%) | <0.001[2] |
| No tea-coffee intake | 2 (1.1%) | 6 (2.3%) | |
| 1-2 cups a day | 67 (35.3%) | 133 (52.0%) | |
| ≥3 cups per day | 121 (63.7%) | 117 (45.7%) | |
| **BMI (kg/m²)** | n (%) | n (%) | <0.001[1] |
| Underweight (<18,5) | 3 (1.6%) | 14 (5.5%) | |
| Normal (18,5-24,9) | 73 (38.4%) | 147 (57.4%) | |
| Overweight (25-29,9) | 66 (34.7%) | 82 (32.0%) | |
| Obese (≥30) | 48 (25.3%) | 13 (5.1%) | |
| **Visceral Fat** | n (%) | n (%) | <0.001[1] |
| Normal | 77 (40.5%) | 176 (68.8%) | |
| High (≥100cm²) | 113 (59.5%) | 80 (31.3%) | |
| **Sleep Quality** | n (%) | n (%) | <0.001[1] |
| Poor sleep quality | 146 (76.8%) | 103 (40.2%) | |
| Good sleep quality | 44 (23.2%) | 153 (59.8%) | |
| **Total** | **190 (100.0%)** | **256 (100.0%)** | |

[1]Pearson chi-square test, [2]Fisher-Freeman-Halton test, *: Spouse-child–parent, friend, sibling, mother-child

No significant differences were observed between sleep quality and mean age (p=0.164) or sex distribution (female: 55.4% vs. 56.9%; p=0.762). Marital status, living arrangements, smoking, alcohol consumption, physical activity, tea/coffee intake, use of blackout curtains, and cell phone use before bedtime showed no significant correlation with sleep quality (p>0.05). However, eating within two hours before sleep (41.4% vs. 29.9%; p=0.002) and night light use (10.4% vs. 3.6%; p=0.010) were significantly higher in physicians with poor sleep quality. The frequency of not eating before sleep was lower in this group (20.9% vs. 35.0%; p=0.002).

Physicians with poor sleep quality had a lower frequency of normal BMI (40.6% vs. 60.4%) and a higher prevalence of obesity (18.9% vs. 7.1%; p<0.001). High visceral fat levels were more common (52.2% vs. 32%; p<0.001), while normal visceral fat levels were less common (47.8% vs. 68.0%; p<0.001). Chronic disease and regular medication use were not associated with sleep quality (p>0.05).

Regarding occupational factors, poor sleep quality was more frequent among those working in surgical branches (42.2% vs. 27.9%; p=0.004) and less frequent among those in internal branches (54.6% vs. 65.5%; p=0.004). The rate of working only standard hours was lower (22.1% vs. 39.6%), while shift and combined work schedules were higher (72.7% vs. 56.9%; p<0.001) in the poor sleep quality group. GERD prevalence was significantly greater in physicians with poor sleep quality (58.6% vs. 22.3%; p<0.001) (Table 3).

Logistic regression analysis showed that the risk of GERD was 1.84 times higher in married physicians compared to singles (OR=1.838; p=0.002). The risk was 2.22 times higher in those living with their spouses (OR=2.227; p=0.002) and 2.21 times higher in those living with spouses and children (OR=2.221; p=0.006). Physicians exercising 1–2 times per week had a 2.57-fold increased risk (OR=2.571; p=0.004), and those who never exercised had a 2.83-fold increased risk (OR=2.833; p=0.002) compared to those exercising ≥3 times per week. Consumption of tomato paste and spicy foods 3–5 times per week increased risk by 2.09 times (OR=2.091; p=0.012), and daily consumption increased risk by 3.95 times (OR=3.949; p<0.001). Eating within two hours before sleep increased the risk by 2.08 and 1.77 times (p=0.004, p=0.023). Overweight physicians had a 3.76-fold risk (OR=3.756; p=0.044), obese physicians a 17.23-fold risk (OR=17.231; p<0.001). High visceral fat increased risk 3.23 times (OR=3.229; p<0.001). Poor sleep quality increased GERD risk by 4.93 times (OR=4.929; p<0.001) (Table 4)

Logistic regression analysis showed that poor sleep quality was 2.32 times higher in physicians who ate within two hours before sleep (OR=2.316; p=0.004) and 1.81 times higher in those who sometimes ate before sleep (OR=1.808; p=0.015). Night time light use increased the risk of poor sleep quality by 3.16 times (OR=3.159; p=0.005). High visceral fat was associated with a 2.32-fold increase (OR=2.323; p<0.001). Physicians in surgical departments had a 3.10-fold higher prevalence of poor sleep quality compared to those in basic medicine

(OR=3.103; p=0.016). Shift plus overtime workers had 2.29 times higher poor sleep quality prevalence than those working only standard hours (OR=2.286; p=0.002). GERD diagnosis increased the risk 4.93 times (OR=4.929; p<0.001) (Table 5).

**Table 3.** Relationships between sociodemographic, health status and occupational characteristics of physicians and sleep quality

| Variable | Poor Sleep Quality (n=249) | Good Sleep Quality (n=197) | *p* |
|---|---|---|---|
| **Food Before Sleep** | n (%) | n (%) | 0.002[1] |
| No | 52 (20.9%) | 69 (35.0%) | |
| Sometimes | 94 (37.8%) | 69 (35.0%) | |
| Yes | 103 (41.4%) | 59 (29.9%) | |
| **Use of a night light** | n (%) | n (%) | 0.010[3] |
| No | 223 (89.6%) | 190 (96.4%) | |
| Yes | 26 (10.4%) | 7 (3.6%) | |
| **BMI (kg/m²)** | n (%) | n (%) | <0.001[1] |
| Underweight (<18,5) | 9 (3.6%) | 8 (4.1%) | |
| Normal (18,5-24,9) | 101 (40.6%) | 119 (60.4%) | |
| Overweight (25-29,9) | 92 (36.9%) | 56 (28.4%) | |
| Obese (≥30) | 47 (18.9%) | 14 (7.1%) | |
| **Visceral adiposity** | n (%) | n (%) | <0.001[1] |
| Normal | 119 (47.8%) | 134 (68.0%) | |
| High (≥100 cm²) | 130 (52.2%) | 63 (32.0%) | |
| **Department** | n (%) | n (%) | 0.004[1] |
| Basic medicine | 8 (3.2%) | 13 (6.6%) | |
| Internal medicine | 136 (54.6%) | 129 (65.5%) | |
| Surgical medicine | 105 (42.2%) | 55 (27.9%) | |
| **Work Shift** | n (%) | n (%) | <0.001[1] |
| Day shift | 55 (22.1%) | 78 (39.6%) | |
| Day shift + night shift | 181 (72.7%) | 112 (56.9%) | |
| Night shift | 13 (5.2%) | 7 (3.6%) | |
| **GERD** | n (%) | n (%) | <0.001[1] |
| No | 103 (41.4%) | 153 (77.7%) | |
| Yes | 146 (58.6%) | 44 (22.3%) | |
| **Total** | **249 (100.0%)** | **197 (100.0%)** | |

BMI: Body mass index; GERD: Gastroesophageal reflux disease. [1]Pearson chi-square test, [2]Fisher-Freeman-Halton test, [3]Chi-square test with Yates continuity correction

**Table 4.** Evaluation of the factors affecting the GERD status of physicians via logistic regression analysis

| Variable | OR (95% CI) | *p* |
|---|---|---|
| **Marital status** | | |
| Single (Ref) | - | - |
| Married | 1.838 (1.254 – 2.706) | 0.002 |
| **A person living in** | | |
| Alone (Ref) | - | - |
| Parents | 1.590 (0.865 – 2.928) | 0.135 |
| Spouse | 2.227 (1.343 – 3.740) | 0.002 |
| Spouse-child | 2.211 (1.264 – 3.905) | 0.006 |
| Other* | 0.502 (0.074 – 2.073) | 0.393 |
| **Physical activity** | | |
| ≥3 per week (Ref) | - | - |
| 1-2 times a week | 2.571 (1.380 – 5.027) | 0.004 |
| No | 2,833 (1,510 - 5,572) | 0.002 |
| **Spicy Sauce Consumption** | | |
| ≤2 times per week (Ref) | - | - |
| 3-5 times a week | 2.091 (1.192 – 3.791) | 0.012 |
| Every day | 3.949 (2.216 – 7.271) | <0.001 |
| **Food Before Sleep** | | |
| No (Ref) | - | - |
| Sometimes | 1.772 (1.087 – 2.916) | 0.023 |
| Yes | 2.079 (1.277 – 3.422) | 0.004 |
| **Tea and coffee consumption** | | |
| No tea-coffee intake (Ref) | - | - |
| 1-2 cups a day | 3.103 (0.699 – 21.468) | 0.171 |
| ≥3 cups per day | 1.511 (0.338 – 10.505) | 0.619 |
| **BMI** | | |
| Underweight (Ref) | - | - |
| Normal weight | 2.317 (0.728 – 10.280) | 0.197 |
| Overweight | 3.756 (1.166 – 16.788) | 0.044 |
| Obese | 17,231 (4.796 – 83.427) | <0.001 |
| **Visceral adiposity** | | |
| Normal (Ref) | - | - |
| High (≥100cm$^2$) | 3.229 (2,188 - 4,797) | <0.001 |
| **PDQI (Sleep Quality)** | | |
| Good sleep quality (Ref) | - | - |
| Poor sleep quality | 4.929 (3,262 - 7,558) | <0.001 |

OR: Odds ratio; CI: Confidence interval; Ref: Reference category; BMI: Body mass index; PDQI: Pittsburgh Sleep Quality Index; n: Number of participants. Ref: Reference Category *: Spouse-child–parent, friend, sibling, mother-child.

**Table 5.** Evaluation of the factors affecting the sleep quality of physicians via logistic regression analysis

| Variable | OR (95% CI) | *p* |
|---|---|---|
| **Food Before Sleep** | | |
| No (Ref) | - | - |
| Sometimes | 1.808 (1.126 – 2.918) | 0.015 |
| Yes | 2.316 (1.436 – 3.766) | <0.001 |
| **Use of a night light** | | |
| No (Ref) | - | - |
| Yes | 3.165 (1.415 – 8.057) | 0.008 |
| **BMI** | | |
| Underweight (Ref) | - | - |
| Normal weight | 0.754 (0.274 – 2.043) | 0.576 |
| Overweight | 1.460 (0.520 – 4.035) | 0.462 |
| Obese | 2.984 (0.960 – 9.316) | 0.057 |
| **Visceral adiposity** | | |
| Normal (Ref) | - | - |
| High (≥100cm$^2$) | 2.324 (1.579 – 3.442) | <0.001 |
| **The department he works in** | | |
| Basic medicine (Ref) | - | - |
| Internal medicine | 1.713 (0.699 – 4.455) | 0.248 |
| Surgical medicine | 3.102 (1.233 – 8.265) | 0.018 |
| **Working order** | | |
| Day shift (Ref) | - | - |
| Day shift + night shift | 2.292 (1.513 – 3.493) | <0.001 |
| Night shift | 2.634 (1.011 – 7.408) | 0.053 |
| **GERD** | | |
| No (Ref) | - | - |
| Yes | 4.929 (3.262 – 7.558) | <0.001 |

OR: Odds ratio; CI: Confidence interval; Ref: Reference category; BMI: Body mass index; GERD, gastroesophageal reflux disease. Ref: Reference Category

## Discussion

This study investigated the prevalence of gastroesophageal reflux disease (GERD) among physicians, an occupational group exposed to irregular working hours, night shifts, heavy workload, and high psychosocial stress, and examined its relationship with sleep quality. Physicians are known to experience greater physiological and psychosocial stress than the general population, which may predispose them to both gastrointestinal and sleep-related disorders. Therefore, understanding the interaction between GERD and sleep disturbances is essential for developing preventive strategies and occupational health interventions.

In the present study, the prevalence of GERD among physicians was 42.6%, which is higher than rates reported in both national and international studies. In Turkey, Mungan et al. reported a GERD prevalence of 24.7% using the GERD-Q, and Ercelep et al. reported a prevalence of 21.7% among hospital workers using the RDQ.[14,15] Internationally, prevalence rates vary, with reports of 57.6% among rescue team healthcare personnel in the United States and 27.4% among physicians in Indonesia. [16,17] These differences may be attributed to variations in diagnostic tools, symptom thresholds, working environments, and occupational stress levels. The relatively high prevalence observed in this study may reflect the cumulative effects of night shifts, irregular meal timing, and sustained clinical and academic stress among physicians.

Significant differences in GERD prevalence were observed according to marital status and living arrangements. While Bert et al. reported a higher prevalence of GERD among married individuals in Italy, [18] Kim et al. found no significant association between marital status and GERD. [19] These inconsistent findings may reflect cultural differences in lifestyle behaviours associated with marriage. In the present study, the higher GERD prevalence among married physicians may be related to late evening meals and increased caloric intake, suggesting that social factors should be evaluated in terms of their influence on lifestyle habits rather than assumed to be inherently protective.

Lifestyle-related factors played a substantial role in GERD development. Physical inactivity increased GERD risk approximately 2.8-fold, while frequent consumption of spicy, fatty, and sauced foods increased the risk up to fourfold. In addition, consumption of tea or coffee within two hours before bedtime and intake exceeding three cups per day were significantly associated with GERD, consistent with previous studies.[20] The demanding work schedules of physicians often lead to irregular meals and reliance on easily accessible but unhealthy food choices, which may exacerbate GERD symptoms.

Obesity and visceral fat accumulation were identified as the strongest predictors of GERD. Obese physicians had approximately a 17-fold higher risk compared with those of normal weight, supporting established pathophysiological mechanisms whereby increased intra-abdominal pressure contributes to lower oesophageal sphincter dysfunction.[21] Moreover, visceral adiposity independently increased GERD risk more than threefold, emphasising the role of metabolically active visceral fat and proinflammatory cytokines in GERD pathogenesis, independent of body mass index.[22]

Poor sleep quality was strongly associated with GERD. Physicians with poor sleep quality had nearly a fivefold higher prevalence of GERD. Similar associations have been reported by Ju et al., who demonstrated that insomnia significantly increased GERD risk,[23] and by Gurges et al., who reported reduced sleep efficiency and total sleep duration among GERD patients.[6] These findings support a bidirectional relationship in which nocturnal reflux symptoms impair sleep quality, while sleep disturbances exacerbate GERD through mechanisms such as autonomic imbalance, delayed gastric emptying, and increased visceral sensitivity.

Poor sleep quality was present in 55.8% of physicians in this study, consistent with findings among healthcare workers in Turkey and Brazil.[24,25] Factors such as eating close to bedtime and sleeping with night lighting were more common among physicians with poor sleep quality. Nogueira et al. demonstrated that shorter meal-to-

sleep intervals negatively affect sleep quality,[26] while Alie et al. reported that sleeping in a dark environment improves sleep outcomes.[27] Additionally, obesity and increased visceral fat were associated with poor sleep quality, in line with evidence suggesting that obesity affects sleep through respiratory, hormonal, and inflammatory pathways.[28] Poor sleep quality was also more prevalent among physicians working in surgical specialities and shift-based schedules, consistent with previous findings.[25]

An important finding of this study is that GERD prevalence was approximately 4.93 times higher among physicians with poor sleep quality. Jansson et al. similarly reported a higher prevalence of GERD among individuals with sleep disorders.[29] This bidirectional relationship may be explained by increased transient lower oesophageal sphincter relaxations, delayed gastric emptying, increased intra-abdominal pressure, autonomic nervous system dysregulation, and heightened pain perception.

From a primary care perspective, GERD and sleep disorders warrant particular attention. Family physicians are uniquely positioned to identify modifiable risk factors, provide lifestyle counselling, and assess sleep quality during routine care. Early recognition and management of GERD may improve sleep health, quality of life, and work productivity among physicians.

Overall, these findings emphasize the importance of addressing occupational stressors, sleep hygiene, and metabolic risk factors to reduce the burden of GERD and sleep disturbances among physicians. Further prospective and interventional studies are required to clarify causal relationships and evaluate the effectiveness of targeted preventive strategies.

Conclusions and Recommendations

Physicians constitute a high-risk group for both gastroesophageal reflux disease and poor sleep quality. Modifiable factors, particularly obesity, visceral fat accumulation, unhealthy dietary habits, physical inactivity, and disrupted sleep patterns, play a central role in this association. Institutional policies aimed at improving working conditions, regulating work hours, facilitating access to healthy food options, and encouraging regular physical activity are essential.

Within family medicine practice, early diagnosis of GERD, lifestyle education, and routine assessment of sleep quality may substantially improve health outcomes and quality of life. Integrating sleep health monitoring and metabolic risk assessment into preventive healthcare strategies for physicians is strongly recommended. Future longitudinal and comprehensive studies are needed to better elucidate causal pathways and to inform effective prevention and management programs.

**Ethical Considerations:** The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1964) and its later amendments. Ethical approval was obtained from the Selcuk University Faculty of Medicine Ethics Committee (Decision No: 2024/366, dated July 16, 2024). Written informed consent was obtained from all participants before their enrollment.

**Conflict of Interest:** The authors declare no conflict of interest.

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# THE IMPACT OF PREGNANCY SPECIFIC DISTRESS ON HAIR LOSS IN WOMEN IN THEIR THIRD TRIMESTER

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## Abstract

**Objectives:** This study aimed to investigate the relationship between pregnancy-specific distress and hair loss in women in their third trimester.

**Materials and Methods:** This cross-sectional study included 138 pregnant women in their third trimester who attended the İstanbul Medipol University Hospital Gynaecology and Obstetrics Clinics. Data were collected through a face-to-face interview using an information form (covering sociodemographic and obstetric history, and hair loss status) and the Tilburg Pregnancy Distress Scale. Results of hematologic and hormonal parameters measured during follow-up were also recorded.

**Results:** Hair loss during pregnancy was reported by 41 participants (29.7%). Based on TPDS total scores, 17 women (12.3%) were classified as at-risk for distress, and 8 (5.8%) according to the Negative Affect (NA) subscale. Women reporting hair loss had higher TPDS total and subscale scores compared to those without hair loss. No significant differences were observed between hair loss and laboratory parameters, suggesting a potential independent role of distress. Number of pregnancies was positively correlated with PI scores ($r=0.284$, $p=0.001$), while age showed a negative correlation with NA scores ($r=-0.184$, $p=0.03$).

**Conclusion:** Pregnant women who complain of hair loss should be screened for pregnancy-specific distress, even in the absence of laboratory abnormalities. Incorporating psychological assessment and support into routine prenatal care may reduce distress-related somatic complaints and improve maternal well-being.

**Keywords:** Hair loss, pregnancy, pregnancy third trimester, psychological distress

## Introduction

Pregnancy is a complicated period of physiological, psychological, and hormonal changes that can have a substantial impact on a woman's body, including her hair.[1] These changes are more noticeable in the third trimester, which is marked by increased hormonal fluctuations and psychological stress, both of which can contribute to hair loss. While hormonal changes during pregnancy, such as prolonged anagen phase due to increased estrogen levels, are usually associated with better hair health, some women report hair loss during this time.[1-5] This variability highlights the multifaceted nature of hair loss during pregnancy, in which physiological, psychological, and dietary variables interact.

Pregnancy-specific distress, encompassing anxiety, depression, and stress related to pregnancy, has been identified as a risk factor for adverse maternal and fetal outcomes, including preterm birth and low birth weight.[6,7] Elevated cortisol concentrations, a biomarker of chronic stress, have been shown to increase progressively across pregnancy, reaching their highest levels in the third trimester.[8,9] In addition, visible bodily changes during pregnancy, including alterations in skin and hair, may further contribute to psychological distress, potentially reinforcing stress-related symptoms.

Despite the known associations between stress and hair loss, the relationship between pregnancy-specific distress and hair loss in pregnant women remains underexplored. Previous studies have primarily focused on postpartum hair loss, while few have addressed this issue during pregnancy itself.[10,11] Therefore, the present study aimed to examine the association between pregnancy-specific distress, assessed using the Tilburg Pregnancy Distress Scale (TPDS), and self-reported hair loss among women in their third trimester. By addressing this gap, the study seeks to contribute to a more comprehensive understanding of stress-related hair changes during pregnancy and to highlight the relevance of psychological well-being in prenatal care.

## Materials and Methods

*Universe and Sample of the Study*

This single-centre, cross-sectional study included women who attended the Department of Gynaecology and Obstetrics at İstanbul Medipol University Hospital for third-trimester pregnancy follow-ups between September 1 and November 1, 2023. All eligible participants underwent the necessary clinical and laboratory evaluations.

The sample size was calculated at a 95% confidence level based on 210 third-trimester pregnancy follow-up visits recorded in the outpatient clinic during the preceding two months, yielding a planned minimum of 137 participants.

After obtaining informed consent, each participant completed a questionnaire administered by the researcher. The questionnaire collected sociodemographic characteristics, obstetric history, and information regarding hair loss. The Tilburg Pregnancy Distress Scale (TPDS) was applied through face-to-face interviews. Laboratory results obtained during third-trimester follow-ups—including haemoglobin (Hb), platelet count (Plt), lymphocyte count (Lym), neutrophil count (Neu), thyroid-stimulating hormone (TSH), free T4 (sT4), and ferritin levels—were recorded from hospital files. These laboratory parameters were used to identify and exclude participants with potential organic or physiological causes of hair loss.

Participants were excluded if they were not in the third trimester, had a history of hair loss, were diagnosed with scalp disorders, had chronic diseases, or were taking regular medications for conditions unrelated to pregnancy. To eliminate physiological causes of hair loss, women with thyroid dysfunction, chronic dermatologic conditions, iron-deficiency–related anemia, or any laboratory abnormality outside normal reference ranges were not included in the study.

*Data Collection Tools*

The data collection form consisted of items assessing age, smoking and alcohol consumption, obstetric history (including number of pregnancies and previous delivery details), use of pregnancy supplements, and self-reported hair loss status. Women who reported experiencing hair loss at any time during the current pregnancy, beginning from early gestation, were considered to have pregnancy-related hair loss.

*Tilburg Pregnancy Distress Scale (TPDS)*

The Tilburg Pregnancy Distress Scale (TPDS) was developed by Pop et al. in 2011 to assess psychological stress specific to pregnancy[12] and includes two subscales: Negative Affect (NA), which assesses pregnancy-related worries, fears, and negative emotional states, and Partner Involvement (PI), which reflects perceived support and involvement of the partner during pregnancy.

The scale was constructed following qualitative interviews with pregnant and postpartum women as well as healthcare professionals, and its final structure was established through factor analysis. It consists of 16 items, each rated on a 4-point Likert scale: “very often” (0 points), “often” (1 point), “sometimes” (2 points), and “rarely or never” (3 points). The total score ranges from 0 to 48, whereas scores for the NA subscale range from 0 to 33, and those for the PI subscale range from 0 to 15.

The Turkish validity and reliability study of the TPDS was conducted by Çapık and Pasinlioğlu.[13] In this study, the scale demonstrated good internal consistency, with a Cronbach's alpha coefficient of 0.83 for the total scale, 0.83 for the NA subscale, and 0.72 for the PI subscale. Factor analyses confirmed the original two-factor structure. Based on the Turkish validation study, the cut-off value for the total TPDS score was determined as 28, while cut-off values were defined as 22.40 for the NA subscale and 10.40 for the PI subscale, corresponding to the 90th percentile of the score distribution. In the present study, the validated Turkish version of the TPDS was used, and scoring was performed in accordance with these established cut-off values.

*Statistical analysis*

All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as frequency (n), percentage (%), mean ± standard deviation, or minimum–maximum values where appropriate. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test.

For group comparisons, the Student's t-test was applied for normally distributed continuous variables, while the Mann–Whitney U test was used for non-normally distributed variables. Comparisons involving more than two groups were performed using the Kruskal–Wallis test. Categorical variables, including distress risk classification according to TPDS cut-off values and the presence of hair loss, were compared using the Chi-square test.

Correlation analyses between continuous variables (such as age, number of pregnancies, and TPDS subscale scores) were performed using Pearson correlation for normally distributed variables and Spearman correlation for non-normally distributed variables. Based on data distribution, the correlation between gravidity and PI scores and the correlation between age and NA scores were evaluated using Spearman's rho. Statistical significance was set at $p < 0.05$.

*Ethical approval*

Ethical approval for the study was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Decision No: 722; Date: August 31, 2023).

## Results

A total of 138 pregnant women were included in the study. Sociodemographic characteristics, smoking and alcohol use, and use of recommended supplements are presented in Table 1.

**Table 1:** Sociodemographic characteristics, obstetric histories, smoking, alcohol use, and supplement intake among participants

| Variables | | Mean ± SD (min, max) |
|---|---|---|
| **Age** | | 30.49±4.71 (20, 42) |
| **Gestational Age** | | 33.95±4.19 (28, 40) |
| **Gravidity** | | 2.12±1.32 (1, 6) |
| **Parity** | | 0.78±0.96 (0, 4) |
| **Abortion** | | 0.36±0.70 (0, 3) |
| | | **n (%)** |
| **Smoking status** | Smoked during pregnancy | 6 (4.3%) |
| | Quit smoking while pregnant | 15 (10.9%) |
| | Never smoked | 117 (84.8%) |
| **Alcohol consumption** | Used alcohol during pregnancy | 2 (1.4%) |
| | Quit alcohol while pregnant | 7 (5.1%) |
| | Never used alcohol | 129 (93.5%) |
| **Use of recommended supplements** | Regularly used | 119 (86.2%) |
| | Did not use | 19 (13.8%) |

The mean TPDS total score was 14.60 ± 7.68. The mean scores of the Negative Affect (NA) and Partner Involvement (PI) subscales were 11.18 ± 6.56 and 3.42 ± 2.21, respectively. Based on TPDS cut-off values, 17 participants (12.3%) were identified as being at risk for pregnancy-related distress according to the total score, and 8 (5.8%) according to the NA subscale. No participants exceeded the risk threshold for the PI subscale.

No significant associations were found between TPDS scores and gestational week, age, gravidity, or parity (p= 0.687, p=0.770, p=0.068, p=0.098). Similarly, distress risk did not differ according to the presence of hair loss or the use of recommended supplements (p= 0.128).

A weak positive correlation was observed between the number of pregnancies and PI scores (r = 0.284, p = 0.001). In contrast, age was weakly and negatively correlated with NA scores (r = −0.184, p = 0.03).

Hair loss during pregnancy was reported by 41 women (29.7%). Among these, most reported the onset of symptoms during the first trimester (n = 32, 23.2%). Hair loss was not associated with gestational age, gravidity, parity, or the number of previous abortions (all p > 0.05).

Comparisons of TPDS total and subscale scores between women with and without hair loss are presented in Table 2. In addition to statistical significance, effect size analyses were performed. The differences in TPDS total and Negative Affect subscale scores showed effect sizes in the small-to-moderate range (r = 0.29 and r = 0.27, respectively). When TPDS cut-off values were used, no differences were found for the total or PI subscale risk classifications (p > 0.05), whereas women with hair loss were more likely to exceed the NA subscale cut-off (p = 0.037).

**Table 2.** Comparison of TPDS total scores and subscale scores between women with and without hair loss complaints

| Variable | Hair Loss (+) (Mean ± SD) | Hair Loss (-) (Mean ± SD) | p value |
|---|---|---|---|
| **TPDS Total Score*** | 18.00±7.77 | 13.16±7.21 | 0.001 |
| **NA Subscale Score*** | 13.85±6.57 | 10.05±6.24 | 0.001 |
| **PI Subscale Score*** | 4.14±2.40 | 3.11±2.06 | 0.019 |

*Mann-Whitney U test, TPDS = Tilburg Pregnancy Distress Scale; NA = Negative Affect; PI = Partner Involvement.

## Discussion

Physiological hormonal changes during pregnancy, particularly the prolonged anagen phase, typically result in thicker hair and a marked reduction in natural hair loss.[2,3,5] Nevertheless, many women report hair loss during pregnancy, indicating that non-hormonal contributors-especially psychological distress-may be associated with hair loss complaints during pregnancy.[14,15] The present study provides evidence supporting this association, demonstrating that women who reported hair loss had significantly higher TPDS total, NA, and PI scores compared with those without hair loss.

In this study, the absence of abnormal laboratory findings and the exclusion of physiological causes of hair loss support the possibility that psychological distress may be associated with hair loss complaints, after minimising potential organic confounding factors. This interpretation is biologically plausible, as previous studies suggest that stress may activate neuroendocrine–immune pathways that can affect the hair cycle.[15,16]

Elevated cortisol levels associated with chronic stress have been shown to prematurely trigger the catagen phase, impairing hair growth and increasing hair loss.[8,9]

Experimental studies also support these mechanisms. Animal models have demonstrated that stress can disrupt hair cycling through activation of the sympathetic nervous system, leading to impaired hair follicle stem cell function.[17] Similarly, a study conducted among medical students during exam periods showed that acute academic stress is associated with reduced hair growth and increased hair loss.[18]

Partner relationships and social support are also known determinants of prenatal distress. Conflict with partners and inadequate perceived support have been associated with higher rates of antenatal anxiety and depressive symptoms, whereas strong partner involvement is protective.[19,20] In a study of 562 pregnant women, dissatisfaction with partner support was associated with a fourfold increase in perinatal distress.[21] Our finding that women with hair loss had higher PI and NA scores suggests that emotional well-being, perceived partner involvement, and hair loss complaints may be interrelated, and that heightened distress, particularly negative affect, may be associated with increased symptom awareness or reporting. These results align with international evidence showing an association between anxiety and hair loss during the perinatal period; for instance, Hirose et al. found significantly higher anxiety scores in women with postpartum hair loss, with a 4.58-fold increased odds of anxiety in those with severe symptoms.[22]

While international research on pregnancy-specific distress and hair loss is growing, there remains a lack of national data from Türkiye. Cultural and social dynamics, healthcare access, and perceptions of cosmetic versus medical symptoms may influence how pregnant women interpret and report hair loss. Therefore, integrating psychosocial screening into antenatal follow-up protocols and generating country-specific evidence would enhance preventive maternal care and mental health support.

Clinically, self-reported hair loss during pregnancy may be considered as a potential indicator of increased pregnancy-related distress, pending confirmation in longitudinal studies, even in the absence of physical abnormalities. Healthcare providers-including physicians, midwives, and nurses-should remain alert to this symptom and offer guidance on modifiable stress-related factors. Previous literature suggests that pregnancy-related psychological distress may be associated with disruptions in homeostasis, altered immune responses, and an increased risk of adverse pregnancy outcomes. [23,24] Thus, supporting mental well-being during pregnancy is as critical as promoting physical health. While these findings have important clinical implications, the use of self-reported hair loss should be considered when interpreting the results. Psychological distress may influence symptom perception and reporting; therefore, the observed association may partly reflect subjective awareness rather than objectively measured hair loss, although self-reported hair loss remains a clinically relevant concern during pregnancy. This reliance on self-reported hair loss may have led to an

overestimation of the observed association, as women with higher psychological distress may be more likely to perceive or report hair loss symptoms.

This study has several limitations. Its cross-sectional, single-centre design limits causal inference and generalizability. The sample size, although adequate, may not have been sufficient to detect weaker associations. In addition, multivariate analyses were not performed because the relatively small sample size and the limited number of participants exceeding distress cut-off values could reduce the stability and reliability of multivariable models. Hair loss was self-reported rather than objectively assessed through clinical methods such as trichoscopy, hair-pull testing, or photographic evaluation, which may introduce recall or reporting bias. Participants' subjective perception of hair loss may differ from clinically measurable hair changes, particularly in the context of heightened psychological distress. Although laboratory parameters such as ferritin, haemoglobin, and thyroid hormones were within normal ranges, other potential contributors were not assessed. In addition, while information on the regular use of recommended pregnancy supplements was recorded, the specific content and dosage of individual components were not analysed separately. Therefore, the results should be interpreted with caution. Future research should employ longitudinal designs with larger and more diverse samples and incorporate objective dermatologic and psychometric evaluations to more fully characterise hair loss mechanisms during pregnancy.

In conclusion, TPDS total scores, NA and PI subscale scores were significantly higher in women with hair loss complaints than in women without hair loss. Ensuring the mental well-being of pregnant women is an essential component of comprehensive prenatal care, given its potential relevance to both physical symptoms and overall maternal health.

Integrating validated tools such as the Tilburg Pregnancy Distress Scale (TPDS) into regular follow-ups may help identify women at higher levels of distress; however, due to the cross-sectional design, these findings should be interpreted as associative rather than causal.

**Ethical Considerations:** Ethical approval for the study was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Decision No: 722; Date: August 31, 2023).

**Conflict of Interest:** The authors declare no conflict of interest.

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# ASSESSMENT OF THE ASSOCIATION BETWEEN INTERNET ADDICTION, E-HEALTHY DIET LITERACY, AND BODY MASS INDEX AMONG ADULTS AGED 18–65 YEARS ATTENDING A UNIVERSITY HOSPITAL FAMILY MEDICINE OUTPATIENT CLINIC

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## Abstract

**Objectives:** This study aimed to examine the association between internet addiction, e-healthy diet literacy (e-HDL), and body mass index (BMI) in adults aged 18–65 years.

**Materials and Methods:** A cross-sectional study was conducted with 378 patients attending a university hospital Family Medicine Outpatient Clinic. Data were collected using a sociodemographic questionnaire, the Internet Addiction Scale (IAS), and the e-Healthy Diet Literacy Questionnaire (e-HDLQ). Statistical analyses were performed using IBM SPSS 22.0.

**Results:** Participants were 52.9% female and 47.1% male, with a mean age of 35.4 ± 12.2 years. BMI was positively correlated with age ($r=0.410$; $p<0.001$). No significant association was found between IAS scores and BMI ($p=0.180$). e-HDLQ scores were significantly higher in overweight individuals than in obese individuals ($p=0.004$). Participants who consumed snacks and main meals while using technological devices had significantly higher IAS scores ($p<0.001$). Snack consumption during device use was most frequent in the overweight group ($p=0.001$).

**Conclusion:** Internet addiction was not directly associated with BMI; however, digital behaviours were linked to eating patterns and screen-based meal consumption. Enhancing e-healthy diet literacy and promoting balanced digital habits may support healthier weight management.

**Keywords:** Internet, internet addiction, healthy nutrition, nutrition literacy, body mass index.

## Introduction

The internet facilitates communication and accelerates access to information; however, uncontrolled use has been associated with physical and psychosocial problems.[1] Prolonged use may result in sedentary behaviour, unbalanced diets, and impaired attention, thereby increasing the risk of obesity, particularly among young people.[2,3]

Internet addiction is defined as increased online activity, restlessness in the absence of access, and disruption of daily functioning.[3] In Türkiye, more than 70% of the population actively uses the internet and social media, while the prevalence of internet addiction has been reported as 6–14%.[4,5]

Nutrition literacy refers to the ability to obtain, evaluate, and apply information about healthy nutrition.[6] The high likelihood of encountering misleading content in digital environments has introduced the concept of "e-nutrition literacy".[7] Insufficient literacy has been associated with unhealthy dietary patterns and obesity.[8]

Obesity, a preventable yet increasing global public health issue, is most commonly assessed by body mass index (BMI).[9] According to the World Health Organisation, 1.9 billion people are overweight, and 650 million are obese.[10] In Türkiye, obesity prevalence is also rising, with major contributors including technological dependence, physical inactivity, and unhealthy diets.[11]

Despite extensive research, studies simultaneously examining internet addiction, nutrition literacy, and obesity are limited. This study aimed to evaluate the relationship between internet addiction, e-nutrition literacy, and BMI among adults aged 18–65 years.

## Materials and Methods

### Study Design and Ethical Approval

This descriptive cross-sectional study was conducted among adults aged 18–65 years attending the Family Medicine Outpatient Clinic of Hatay Mustafa Kemal University Hospital to evaluate the relationship between internet addiction, e-nutrition literacy, and BMI. Ethical approval was obtained from the Non-Interventional Research Ethics Committee of Hatay Mustafa Kemal University (decision no: 12/36, 20.11.2024).

### Sample and Participants

The study population included residents of Antakya and Defne districts (Hatay) aged 18–65 years. According to 2022 data from the Turkish Statistical Institute, this group comprised 383,087 individuals. Assuming 20%

prevalence of internet addiction and 95% confidence level, the required sample size was calculated as 246. With an additional 10% margin for attrition, the target was 271. Data were collected from a total of 378 participants who met the inclusion criteria.

Inclusion criteria: age 18–65, literacy, voluntary participation, and ability to read and understand the questionnaire.

Exclusion criteria: <18 or >65 years of age, illiteracy, or incomplete questionnaires.

**Data Collection**

Survey data were collected face-to-face and online (via QR code) at the Family Medicine Outpatient Clinic of Hatay Mustafa Kemal University Hospital. All measurements were conducted in person: height with a wall-mounted tape and weight with a digital scale, with participants barefoot and upright.

Instruments: a 29-item sociodemographic questionnaire, the Internet Addiction Scale (IAS), and the e-Healthy Diet Literacy Questionnaire (e-HDLQ). Participants were verbally informed and provided written consent.

Internet Addiction Scale (IAS): Developed by Hahn and Jerusalem and adapted into Turkish by Şahin and Korkmaz. The 19-item Likert-type scale yields a total score of 19–95; higher scores indicate greater addiction. It includes three subscales: loss of control, desire to remain online, and impairment of social relations. Cronbach's alpha = 0.858.[12]

e-Healthy Diet Literacy Questionnaire (e-HDLQ): Developed by Van Duong et al. (2020) and adapted into Turkish by Onbaşı and Türker. The 15-item scale includes five subdimensions: access, understanding, evaluation, application, and digital competence. The maximum score is 71, with higher scores indicating greater literacy. Cronbach's alpha = 0.77.[13]

**Statistical Analysis**

Data were analysed using IBM SPSS Statistics 25.0. Descriptive statistics included mean, standard deviation, median (Q1–Q3), frequency, and percentage. Continuous variables were compared using t-test, Mann-Whitney U, ANOVA, or Kruskal-Wallis tests, with Tamhane or Bonferroni-corrected post-hoc tests as appropriate. Relationships between continuous variables were assessed with Pearson correlation, and categorical variables with chi-square tests. Statistical significance was set at $p<0.05$.

## Results

A total of 378 participants were included, of whom 52.9% (n=200) were female, and 47.1% (n=178) were male. Their ages ranged from 18 to 65 years, with a mean of 35.4 ± 12.2.

Sociodemographic characteristics showed that 52.4% (n=198) were single, 69.8% (n=264) were university graduates, 63.0% (n=238) were employed, and 47.6% (n=180) reported income exceeding expenses. Chronic disease was present in 22.2% (n=84).

Regarding lifestyle, 41.5% (n=157) were smokers and 35.7% (n=135) consumed alcohol. More than half (50.3%, n=190) reported no physical activity. In addition, 71.7% (n=271) stated that they usually slept at night and woke up in the morning, indicating a regular sleep routine.

According to BMI categories, 47.4% (n=179) were normal weight, 38.6% (n=146) overweight, and 14.0% (n=53) obese (Table 1).

Dietary habits showed that 57.9% (n=219) reported having a balanced diet, and 66.1% (n=250) considered their nutrition knowledge sufficient. Eating behaviours in front of technological devices revealed that 45.0% (n=170) consumed only snacks, while 29.9% (n=113) consumed both snacks and main meals. Trusted nutrition information sources were identified as physicians/dietitians (37.6%), social media/internet/television (35.4%), and family/friends (27.0%).

Social media use was reported by 91.8% (n=347). Daily internet use was reported by 49.2% (n=186), and 9.3% (n=35) used it ≥8 hours. Nearly half (44.4%, n=168) searched specifically for nutrition-related content, and 66.1% (n=250) were interested in such posts (Table 2).

Across BMI groups, significant differences were observed for age, sex, education, chronic disease, physical activity, trusted nutrition sources, eating behaviours in front of devices, and e-HDLQ scores. Overweight and obese participants were older ($p<0.001$), more often male ($p<0.001$), and more frequently primary/secondary school graduates ($p=0.007$). Chronic disease was more prevalent in overweight and obese groups compared with normal weight, and most common in the obese group ($p<0.001$). Participants engaging in ≥5 days of weekly physical activity were more common among overweight and obese individuals ($p=0.008$).

**Table 1.** Sociodemographic characteristics of the participants

| Variables | n=378 |
|---|---|
| **Age (years), Mean ± SD** | 35.4 ± 12.2 |
| **Gender, n (%)** | |
| **Male** | 178 (47.1) |
| **Female** | 200 (52.9) |
| **Marital Status, n (%)** | |
| **Married** | 180 (47.6) |
| **Single** | 198 (52.4) |
| **Educational Status, n (%)** | |
| **Primary/Secondary Education** | 114 (30.2) |
| **University** | 264 (69.8) |
| **Employment Status, n (%)** | |
| **Employed** | 238 (63.0) |
| **Unemployed** | 140 (37.0) |
| **Income Status, n (%)** | |
| **Income is less than expenses** | 122 (32.3) |
| **Income equal to expenses** | 76 (20.1) |
| **Income greater than expenses** | 180 (47.6) |
| **BMI, n (%)** | |
| **Normal** | 179 (47.4) |
| **Overweight** | 146 (38.6) |
| **Obese** | 53 (14.0) |
| **Chronic Disease Status, n (%)** | |
| **Yes** | 84 (22.2) |
| **No** | 294 (77.8) |
| **Smoking, n (%)** | |
| **Yes** | 157 (41.5) |
| **No** | 221 (58.5) |
| **Alcohol Use, n (%)** | |
| **Yes** | 135 (35.7) |
| **No** | 243 (64.3) |
| **Frequency of Physical Activity, n (%)** | |
| **None** | 190 (50.3) |
| **A few days per week** | 93 (24.6) |
| **≥5 days per week** | 95 (25.1) |
| **Sleep Pattern, n (%)** | |
| **Spending time on games/TV at night and going to bed late.** | 107 (28.3) |
| **Sleeping at night and waking up in the morning** | 271 (71.7) |

n: number, BMI: Body Mass Index

**Table 2.** Distribution of participants' nutrition knowledge and digital media use habits

| Variables | n (%) |
|---|---|
| **Do you think you follow an adequate and balanced diet?** | |
| **Yes** | 219 (57.9) |
| **No** | 159 (42.1) |
| **Do you think your level of nutrition knowledge is sufficient?** | |
| **Yes** | 250 (66.1) |
| **No** | 128 (33.9) |
| **Eating habits in front of technological devices (computer, tablet, phone, etc.)** | |
| **I do not eat in front of such devices** | 95 (25.1) |
| **I only consume snacks in front of such devices** | 170 (45.0) |
| **I consume all my meals, including main meals, in front of such devices** | 113 (29.9) |
| **Trusted sources of nutrition information** | |
| **Social media / Internet / Television** | 134 (35.4) |
| **Friends / Family / Acquaintances** | 102 (27.0) |
| **Doctor / Dietitian** | 142 (37.6) |
| **Use of social media, n (%)** | |
| **Yes** | 347 (91.8) |
| **No** | 31 (8.2) |
| **Daily internet usage time, n (%)** | |
| **Not every day** | 186 (49.2) |
| **1-3 hours** | 116 (30.7) |
| **4-5 hours** | 26 (6.9) |
| **6-8 hours** | 15 (4.0) |
| **≥8 hours** | 35 (9.3) |
| **Do you specifically search for nutrition-related posts while browsing the internet? , n (%)** | |
| **Yes** | 168 (44.4) |
| **No** | 210 (55.6) |
| **Do nutrition-related posts you encounter on the internet and/or social media attract your attention? , n (%)** | |
| **Yes** | 250 (66.1) |
| **No** | 128 (33.9) |

n = Number

Trusted sources of nutrition information differed significantly (p=0.014). Post-hoc analysis showed that fewer obese participants relied on social media/internet/television compared with the other groups. Eating behaviours also differed (p=0.001): snack consumption in front of devices was highest in the overweight group, while the obese group showed higher rates than normal-weight individuals.

e-HDLQ scores were significantly higher among overweight participants compared with obese (p=0.004), whereas IAS scores did not differ across BMI categories (p=0.180) (Table 3).

By sociodemographic factors, only eating behaviour in front of devices was associated with IAS. Post-hoc analysis indicated that participants consuming only snacks or both snacks and main meals had higher IAS scores than those who did not eat while online (p<0.001). No significant differences were observed in e-HDLQ scores across these groups (Table 4).

Correlation analyses showed a positive relationship between BMI and age (r=0.410, p<0.001). Weak, non-significant correlations were found between BMI and IAS (r=0.049, p=0.346) and between BMI and e-HDLQ (r=–0.011, p=0.826) (Table 5).

Physical activity levels varied significantly by age, marital status, parenthood, education, income, chronic disease, dietary perception, nutrition knowledge, and internet use. Participants active ≥5 days/week were older (p=0.046) and more often single, while those active a few days/week were more often married (p=0.002). Having children was associated with higher rates of ≥5 days of activity (p=0.009).

Higher rates of ≥5 days/week activity were also reported among those with lower education (p=0.002), lower income (p=0.009), and chronic disease (p=0.006). Participants active a few days/week more frequently reported balanced diets (p<0.001) and sufficient nutrition knowledge (p=0.025). Daily internet use ≥8 hours was significantly more frequent among those active ≥5 days/week (p=0.002) (Table 6).

IAS scores were significantly higher in participants with children compared with those without (p=0.002), whereas no significant differences were observed in e-HDLQ scores by parental status (p=0.591).

**Table 3.** Comparison of participants' basic variables according to BMI groups

| Variables | BMI | | | p-value |
|---|---|---|---|---|
| | Normal | Overweight | Obese | |
| **Age, Median (Q1–Q3)** | 26 (24 - 36) | 38 (28 - 52) | 39 (30 - | **<0.001[a,b]** |
| **Sex, n (%)** | **n (%)** | **n (%)** | **n (%)** | |
| **Male** | 66 (36.9) | 83 (56.8) | 29 (54.7) | **<0.001[a,b]** |
| **Female** | 113 (63.1) | 63 (43,2) | 24 (45.3) | |
| **Education** | | | | |
| **Primary/Secondary** | 40 (22.3) | 55 (37.7) | 19 (35.8) | **0.007[a,b]** |
| **University** | 139 (77.7) | 91 (62.3) | 34 (64.2) | |
| **Employment Status** | | | | |
| **Employed** | 116 (64.8) | 92 (63.0) | 30 (56.6) | 0.554 |
| **Unemployed** | 63 (35.2) | 54 (37.0) | 23 (43.4) | |
| **Chronic Disease** | | | | |
| **Yes** | 23 (12.8) | 41 (28.1) | 20 (37.7) | **<0.001[a,b,c]** |
| **No** | 156 (87.2) | 105 (71.9) | 33 (62.3) | |
| **Physical Activity Frequency** | | | | |
| **None** | 91 (50.8) | 72 (49.3) | 27 (50.9) | **0.008[a,b]** |
| **A few days per week** | 56 (31.3) | 29 (19.9) | 8 (15.1) | |
| **≥5 days per week** | 32 (17.9) | 45 (30.8) | 18 (34.0) | |
| **Sleep Pattern** | | | | |
| **Spending time on games/TV at night and going to bed late** | 47 (26.3) | 42 (28.8) | 18 (34.0) | 0.543 |
| **Sleeping at night, waking up in the morning** | 132 (73.7) | 104 (71.2) | 35 (66.0) | |
| **Trusted Sources of Nutrition Information** | | | | |
| **Social media / Internet / Television** | 75 (41.9) | 50 (34.2) | 9 (17.0) | **0.014[b,c]** |
| **Friends / Family / Acquaintances** | 44 (24.6) | 37 (25.3) | 21 (39.6) | |
| **Doctor / Dietitian** | 60 (33.5) | 59 (40.4) | 23 (43.4) | |
| **Social Media Use** | | | | |
| **Yes** | 170 (95.0) | 131 (89.7) | 46 (86.8) | 0.082 |
| **No** | 9 (5.0) | 15 (10.3) | 7 (13.2) | |
| **Eating habits in front of technological devices (computer, tablet, phone, etc.)** | | | | |
| **I do not eat in front of such devices** | 51 (28.5) | 29 (19.9) | 15 (28.3) | |
| **I only consume snacks in front of such devices** | 63 (35.2) | 85 (58.2) | 22 (41.5) | **0.001[a,b,c]** |
| **I consume all my meals, including main meals, in front of such devices** | 65 (36.3) | 32 (21.9) | 16 (30.2) | |
| **IAS total score, Median (Q1–Q3)** | 70 (55 - 76) | 73 (59 - 76) | 69 (55 - | 0.180 |
| **e-HDLQ total score, Mean ± SD** | 44.3 ± 7.2 | 45.7 ± 6.3 | 42.0 ± 8.2 | **0.004[c]** |

n = Number, SD = Standard Deviation, BMI = Body Mass Index, e-HDLQ = e-Healthy Diet Literacy Questionnaire.
[a]: Normal vs Overweight, [b]: Normal vs Obese, [c]: Overweight vs Obese. p-values were obtained using chi-square or Kruskal-Wallis tests (post-hoc: Tamhane or Bonferroni-corrected Mann-Whitney U). IAS scores ranged from 19 to 94, with a mean of 66.5 ± 15.4. e-HDLQ scores ranged from 23 to 62, with a mean of 44.5 ± 7.1.

**Table 4.** Comparison of IAS and e-HDLQ scores by sociodemographic characteristics

| Variables | IAS Mean±SD Median (Q1–Q3) | p-value | e-HDLQ Mean±SD Median (Q1–Q3) | p-value |
|---|---|---|---|---|
| **Sex** | | | | |
| **Male** | 65.4 ± 16.0 | 0.199 | 45.1 ± 6.9 | 0.117 |
| **Female** | 67.4 ± 14.8 | | 44.0 ± 7.2 | |
| **Employment status** | | | | |
| **Employed** | 66.8 ± 15.9 | 0.537 | 44.5 ± 7.0 | 0.979 |
| **Unemployed** | 65.8 ± 14.5 | | 44.5 ± 7.4 | |
| **Physical Activity Frequency** | | | | |
| **None** | 65.9 ± 15.5 | 0.365 | 44.5 ± 7.3 | 0.951 |
| **A few days per week** | 65.6 ± 17.2 | | 44.7 ± 6.7 | |
| **≥5 days per week** | 68.4 ± 13.1 | | 44.4 ± 7.2 | |
| **Smoking** | | | | |
| **Yes** | 65.7 ± 15.3 | 0.404 | 44.6 ± 6.8 | 0.807 |
| **No** | 67.0 ± 15.5 | | 44.4 ± 7.3 | |
| **Alcohol use** | | | | |
| **Yes** | 65.7 ± 16.1 | 0.452 | 44.2 ± 7.0 | 0.596 |
| **No** | 66.9 ± 15.0 | | 44.7 ± 7.2 | |
| **Sleep Pattern** | | | | |
| **Spending time on games/TV at night and going to bed late** | 63.9 ± 17.2 | 0.061 | 44.2 ± 7.8 | 0.552 |
| **Sleeping at night, waking up in the morning** | 67.5 ± 14.5 | | 44.6 ± 6.8 | |
| **Education** | | | | |
| **Primary/Secondary** | 72.5 (59.0 - 75.0) | 0.996 | 44.4 ± 7.0 | 0.892 |
| **University** | 70.0 (55.5 - 77.0) | | 44.5 ± 7.2 | |
| **Chronic Disease** | | | | |
| **Yes** | 73.0 (63.5 – 75.0) | 0.376 | 44.3 ± 7.0 | 0.788 |
| **No** | 70.0 (56.0 – 76.0) | | 44.6 ± 7.2 | |
| **Trusted Sources of Nutrition Information** | | | | |
| **Social media / Internet / Television** | 65.4 ± 16.3 | 0.611 | 44.7 ± 6.9 | 0.156 |
| **Friends / Family / Acquaintances** | 66.8 ± 15.4 | | 44.4 ± 7.3 | |
| **Doctor / Dietitian** | 67.2 ± 14.6 | | 44.4 ± 7.2 | |
| **Social Media Use** | | | | |
| **Yes** | 70.0 (56.0 – 76.0) | 0.748 | 44.7 ± 7.2 | 0.142 |
| **No** | 75.0 (60.0 – 75.0) | | 42.7 ± 6.2 | |
| **Eating habits in front of technological devices (computer, tablet, phone, etc.)** | | | | |
| **I do not eat in front of such devices** | 62.0 (50.0 – 72.0) | **<0.001** [x, y] | 43.4 ± 6.8 | 0.228 |
| **I only consume snacks in front of such devices** | 75.0 (65.0 – 77.0) | | 44.9 ± 6.9 | |
| **I consume all my meals, including main meals, in front of such devices** | 69.0 (54.0 – 76.0) | | 44.8 ± 7.6 | |

p-values were obtained using the Kruskal–Wallis test. For significant variables, pairwise comparisons were performed with the Mann–Whitney U test with Bonferroni correction. [x]: Significant difference between those who never ate in front of devices and those who consumed only snacks. [y]: Significant difference between those who never ate in front of devices and those who consumed all meals, including main meals.

**Table 5.** Evaluation of the relationship between BMI and age, IAS, and e-HDLQ total scores

| | | Age | IAS Total Score | e-HDLQ Total Score |
|---|---|---|---|---|
| **BMI** | r | 0.410** | 0.049 | -0.011 |
| | p | **<0.001** | 0.346 | 0.826 |

** r: Correlation coefficient. p-values were obtained using the Pearson correlation test. p < 0.001 indicates statistical significance.

**Table 6.** Comparison of demographic characteristics, dietary habits, and internet use by physical activity level

| Variables | Physical Activity | | | p-value |
|---|---|---|---|---|
| | None | A few days per week | ≥5 days per week | |
| **Age, Median (Q1–Q3)** | 32 (25 - 43) | 29 (24 - 42) | 36 (25 -52) | **0.046** |
| **Sex** | **n (%)** | **n (%)** | **n (%)** | |
| **Male** | 88 (46.3) | 46 (49.5) | 44 (46.3) | 0.870 |
| **Female** | 102 (53.7) | 47 (50.5) | 51 (53.7) | |
| **Marital status** | | | | |
| **Married** | 93 (48.9) | 55 (59.1) | 32 (33.7) | **0.002** |
| **Single** | 97 (51.1) | 38 (40.9) | 63 (66.3) | |
| **Having children** | | | | |
| **Yes** | 82 (43.2) | 37 (39.8) | 57 (60.0) | **0.009** |
| **No** | 108 (56.8) | 56 (60.2) | 38 (40.0) | |
| **Education** | | | | |
| **Primary/Secondary** | 50 (26.3) | 22 (23.7) | 42 (44.2) | **0.002** |
| **University** | 140 (73.7) | 71 (76.3) | 53 (55.8) | |
| **Employment status** | | | | |
| **Employed** | 125 (65.8) | 60 (64.5) | 53 (55.8) | 0.241 |
| **Unemployed** | 65 (34.2) | 33 (35.5) | 42 (44.2) | |
| **Income Status** | | | | |
| **Income is less than expenses** | 51 (26.8) | 26 (28.0) | 45 (47.4) | **0.009** |
| **Income equal to expenses** | 39 (20.5) | 21 (22.6) | 16 (16.8) | |
| **Income greater than expenses** | 100 (52.6) | 46 (49.5) | 34 (35.8) | |
| **Chronic Disease** | | | | |
| **Yes** | 46 (24.2) | 10 (10.8) | 28 (29.5) | **0.006** |
| **No** | 144 (75.8) | 83 (89.2) | 67 (70.5) | |
| **Smoking** | | | | |
| **Yes** | 86 (45.3) | 33 (35.5) | 38 (40.0) | 0.275 |
| **No** | 104 (54.7) | 60 (64.5) | 57 (60.0) | |
| **Alcohol use** | | | | |
| **Yes** | 78 (41.1) | 31 (33.3) | 26 (27.4) | 0.065 |
| **No** | 112 (58.9) | 62 (66.7) | 69 (72.6) | |
| **Sleep Pattern** | | | | |
| **Spending time on games/TV at night and going to bed late** | 64 (33.7) | 20 (21.5) | 23 (24.2) | 0.060 |
| **Sleeping at night, waking up in the morning** | 126 (66.3) | 73 (78.5) | 72 (75.8) | |
| **Do you think you follow an adequate and balanced diet?** | | | | |
| **Yes** | 110 (57.9) | 67 (72.0) | 42 (44.2) | **<0.001** |
| **No** | 80 (42.1) | 26 (28.0) | 53 (55.8) | |
| **Do you think your level of nutrition knowledge is sufficient?** | | | | |
| **Yes** | 128 (67.4) | 69 (74.2) | 53 (55.8) | **0.025** |
| **No** | 62 (32.6) | 24 (25.8) | 42 (44.2) | |
| **Dietary habits** | | | | |
| **I do not skip meals; I have three meals a day.** | 52 (27.4) | 27 (29.0) | 34 (35.8) | 0.058 |
| **I only have two meals a day.** | 21 (11.1) | 7 (7.5) | 17 (17.9) | |
| **I have only one main meal and replace the others with snacks.** | 117 (61.6) | 59 (63.4) | 44 (46.3) | |
| **Eating habits in front of technological devices (computer, tablet, phone, etc.)** | | | | |
| **I do not eat in front of such devices** | 49 (25.8) | 27 (29.0) | 19 (20.0) | 0.095 |
| **I only consume snacks in front of such devices** | 77 (40.5) | 39 (41.9) | 54 (56.8) | |

| | | | | |
|---|---|---|---|---|
| **I consume all my meals, including main meals, in front of such devices** | 64 (33.7) | 27 (29.0) | 22 (23.2) | |
| **Trusted Sources of Nutrition Information** | | | | |
| **Social media / Internet / Television** | 74 (38.9) | 37 (39.8) | 23 (24,2) | 0,118 |
| **Friends / Family / Acquaintances** | 47 (24.7) | 23 (24.7) | 32 (33.7) | |
| **Doctor / Dietitian** | 69 (36.3) | 33 (35.5) | 40 (42.1) | |
| **Social Media Use** | | | | |
| **Yes** | 177 (93.2) | 88 (94.6) | 82 (86.3) | 0.073 |
| **No** | 13 (6.8) | 5 (5.4) | 13 (13.7) | |
| **Daily internet usage time** | | | | |
| **Not every day** | 95 (50.0) | 44 (47.3) | 47 (49.5) | **0.002** |
| **1-3 hours** | 60 (31.6) | 36 (38.7) | 20 (21.1) | |
| **4-5 hours** | 19 (10.0) | 3 (3.2) | 4 (4.2) | |
| **6-8 hours** | 4 (2.1) | 4 (4.3) | 7 (7.4) | |
| **≥8 hours** | 12 (6.3) | 6 (6.5) | 17 (17.9) | |

p-values were calculated using Chi-square or Kruskal-Wallis test, with post-hoc analysis performed where appropriate.

## Discussion

This study examined the associations between internet addiction (IAS) and e-healthy diet literacy (e-HDL) scores and BMI, lifestyle factors, dietary habits, and sociodemographic characteristics in adults. To our knowledge, studies evaluating these three variables simultaneously are limited, suggesting that this research may contribute to the existing literature.

With the rapid shift of social interactions toward digital environments in the 21st century, digital platforms have assumed a prominent role in shaping dietary norms. A substantial proportion of food-related content shared on social media consists of unhealthy foods, indicating that repeated exposure to energy-dense products may influence eating behaviours. [14]

The literature suggests that longer social media use is associated with increased unhealthy dietary behaviours. Given the high duration of internet and social media use in Türkiye, this exposure appears widespread at the population level.[4,15] In the present study, the high proportion of active social media users and participants interested in nutrition-related content supports the potential influence of digital environments on nutrition literacy and dietary behaviours. These findings are consistent with previous research.

Previous studies have reported a positive association between age and BMI. Kiadaliri et al. demonstrated that obesity prevalence is lower among younger individuals and increases with advancing age in both men and women.[9] Similarly, in this study, overweight and obese individuals had higher mean ages than normal-weight individuals, and BMI increased with age. The higher prevalence of overweight in middle age may be related

to age-related metabolic decline, reduced physical activity, and lifestyle changes, supporting age as an important risk factor for weight gain.

Gender-based differences in the relationship between e-HDL and BMI have been reported, with men more frequently classified as overweight or pre-obese and women more commonly within the normal BMI range.[4,16] Consistent with these findings, women in our study were predominantly of normal weight, whereas men were more often overweight or obese. Higher body-weight awareness and stronger motivation for weight control among women may partially explain this pattern, whereas more irregular dietary habits and comparatively lower weight-related awareness among men may contribute. These findings highlight gender as a potentially important determinant of dietary behaviours and weight status.

Regarding educational level, overweight and obesity were more prevalent among individuals with primary and secondary education, whereas university graduates were more frequently within the healthy weight range. This finding is consistent with studies indicating that obesity prevalence decreases as educational level increases.[17] Higher education may facilitate access to accurate information on nutrition and physical activity and enhance the ability to translate knowledge into behaviour, thereby supporting healthy weight control.[18]

Although physical activity is generally reported to decline and obesity risk to increase with age[18], some studies indicate that activity levels may rise again in later life.[19] In this study, individuals engaging in physical activity on ≥5 days per week had a higher mean age, possibly reflecting increased health awareness and a greater tendency toward lifestyle modification in later years. The relatively high educational level of participants may have further contributed to increased awareness of physical activity and healthy living.

Single individuals were more physically active than married individuals, possibly due to greater flexibility in allocating time to physical activity. In contrast, increased work and family responsibilities among married individuals may contribute to a more sedentary lifestyle.

Interestingly, individuals with children reported higher rates of engaging in physical activity on ≥5 days per week, differing from studies suggesting that parenthood reduces activity levels.[20] This discrepancy may reflect sociocultural characteristics of the sample and the perception of physical activity as daily-life movement rather than structured exercise. Activities performed with children may also increase overall movement levels among parents.

The relationship between education and physical activity showed partial divergence from the literature.[18] Individuals with lower educational attainment had higher rates of engaging in frequent physical activity, possibly due to employment in physically demanding occupations or the perception of activity as routine

daily movement rather than planned exercise. In addition, the lack of a detailed assessment of activity type and reliance on self-reported data may have limited the accurate reflection of actual activity levels.

Physically active individuals were more frequently concentrated in the lower-income group. Previous studies have reported inconsistent findings regarding the relationship between income, obesity, and physical activity, with some identifying no association between income and BMI.[21] In this study, higher activity levels among lower-income individuals may be explained by occupational physical demands and daily movement patterns rather than structured exercise. Studies evaluating only planned exercise may underestimate total physical activity levels.

Physically active participants were more likely to perceive their diet as adequate and balanced and reported higher perceived nutrition knowledge. This aligns with literature demonstrating a positive association between physical activity and healthy dietary behaviours. [22] Greater health motivation and awareness among active individuals may support both healthier eating behaviours and higher nutrition knowledge.

Chronic disease was identified in 22.2% of participants and was more prevalent among overweight and obese individuals, particularly in the obese group, consistent with the established association between obesity and conditions such as type 2 diabetes and hypertension.[11] However, individuals with chronic disease reported higher rates of frequent physical activity, which may reflect increased health awareness and lifestyle modifications following diagnosis. Medication-related effects on metabolism, appetite, and activity levels may also contribute to this relationship.

The higher prevalence of frequent physical activity among overweight and obese individuals compared with normal-weight individuals is noteworthy. Although increased physical activity is generally expected to reduce BMI, this finding may indicate that individuals with higher BMI have recently increased their activity levels as part of weight control efforts. Previous research has suggested that post-overeating discomfort or increased awareness may motivate greater physical activity.[17]

Health professionals and mass media were the most trusted sources of nutrition information. Obese individuals were less likely to regard social media and the internet as reliable sources, possibly reflecting greater caution toward online nutrition content. The relatively high educational and socioeconomic status of participants may have contributed to greater awareness of misinformation and preference for expert guidance.

From a behavioural perspective, eating in front of technological devices was common and more pronounced among overweight and obese groups. Prolonged screen exposure has been associated with unhealthy food

choices and adverse lifestyle patterns.[3] Eating while using screens may contribute to weight gain through mechanisms such as distraction, impaired portion control, and unintentional increases in energy intake.

No significant association was found between BMI and IAS scores. The literature reports mixed findings, with some studies suggesting that intensive internet use increases the likelihood of overweight or obesity, while others report no association.[23,24] The absence of a relationship in this study suggests that the impact of internet use on weight status may depend on duration, content type, and accompanying lifestyle behaviours.

IAS scores were not significantly associated with gender, employment status, lifestyle factors, education, or chronic disease. Similarly, no association was found between IAS scores and physical activity. However, individuals engaging in physical activity on ≥5 days per week reported higher rates of ≥8 hours of daily internet use, indicating that physical activity alone may not limit screen exposure. This finding suggests that internet use behaviour may be influenced by factors beyond physical activity.[23]

While Saldıran reported no effect of physical activity on internet addiction in Türkiye [25], Khan et al. observed decreased activity with increasing addiction.[26] This inconsistency may reflect conceptual differences between internet use and internet addiction or the possibility that individuals can remain physically active while consuming digital content intensively. Given that most participants were university graduates, internet use may have been primarily education- or work-related. Therefore, physical activity and digital addiction do not necessarily demonstrate an inverse relationship.

Although some studies suggest that smokers may be more prone to internet addiction[2], others report no association.[27] Similarly, no relationship was found between smoking and IAS scores in this study. While higher internet addiction has been reported among individuals with alcohol or substance dependence [2], no association was identified here. The lack of a detailed assessment of alcohol dependency may explain this finding.

Participants who consumed both snacks and main meals in front of screens had higher IAS scores, suggesting that an online-oriented lifestyle may reinforce screen-based eating behaviours. Visually oriented platforms have been shown to influence dietary habits, and prolonged screen time has been associated with eating disorders and obesity.[14,28]

Nutrition literacy plays a central role in adopting healthy eating behaviours by enabling access to accurate information and its translation into practice. In this study, e-HDL scores were not significantly associated with gender, employment status, lifestyle factors, or chronic disease. Although some variation in e-HDL scores across BMI groups was observed, differences were not statistically significant, indicating the need for further evaluation using larger samples and diverse measurement approaches. Previous studies have reported

heterogeneous findings, with some identifying a negative correlation between BMI and food literacy[29], others reporting higher literacy among underweight individuals[8], and some indicating increased risk among both underweight and overweight adolescents.[30] Such heterogeneity may be attributed to differences in measurement tools, age groups, and cultural contexts. Our findings suggest that beyond knowledge itself, barriers influencing the translation of knowledge into behaviour—such as habits, environmental exposure, and resource constraints—may play a critical role.

*Limitations*

This study has limitations. It was conducted in a single tertiary hospital in Hatay, restricting generalizability to the wider Turkish population. Furthermore, exercise type and frequency were not assessed in detail, and reliance on self-reported measures may have introduced bias. Future multicenter studies with larger and more diverse samples are warranted to confirm and expand these findings.

In conclusion, this study investigated the relationship between internet addiction, e-HDLQ, and BMI among individuals aged 18–65 years. Internet addiction scores were higher among participants who reported eating in front of devices, particularly those who consumed snacks, a behaviour more common in overweight and obese groups.

A significant relationship was observed between e-HDLQ and BMI, with overweight participants having higher scores than obese participants, suggesting that body weight may be a significant predictor of e-nutrition literacy. The findings indicate that digital habits influence dietary behaviours.

Given the ease of access to both accurate and misleading information in digital environments, health risks may arise. Therefore, monitoring and regulating online health-related content by public health authorities is of great importance. Preventive strategies should focus on evaluating screen time and usage patterns at the individual level, controlling duration of use, and enhancing nutrition literacy.

It is further recommended to implement age- and occupation-specific awareness programs and to provide regular nutrition literacy training in community and family health centres to promote healthier dietary practices.

**Ethical Considerations:** This descriptive cross-sectional study was conducted among adults aged 18–65 years attending the Family Medicine Outpatient Clinic of Hatay Mustafa Kemal University Hospital to evaluate the relationship between internet addiction, e-nutrition literacy, and BMI. Ethical approval was obtained from the Non-Interventional Research Ethics Committee of Hatay Mustafa Kemal University (decision no: 12/36, 20.11.2024).

**Conflict of Interest:** The authors declare no conflict of interest.

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# THE RELATIONSHIP BETWEEN HEALTH LITERACY AND THE RATIONAL USE OF MEDICINES AMONG INDIVIDUALS WITH CHRONIC DISEASES

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## Abstract

**Objectives:** This study aimed to establish the connection between health literacy and the appropriate use of medications among individuals suffering from chronic diseases.

**Materials and Methods:** This descriptive and correlational study examined individuals with at least one chronic disease who presented to family medicine units in the Bucak District of Türkiye. The required sample size was calculated at 95% confidence and a 5% margin of error, and 386 participants were needed. Ultimately, data were collected from 488 participants. Data were obtained using the 'Health Literacy Scale' and the ' Rational Use of Medicines Scale'.

**Results:** A mean score of 35.89±5.38 was achieved on the rational use of medicines, indicating a moderate level of awareness. The mean Health Literacy Scale score was 104.66 ± 15.49, indicating a high level of health literacy among participants. A test of the connection between health literacy and sensible drug use showed a strong link ($r=0.60$, $p<.001$). Health literacy and rational use of medicines scores differed significantly according to age, educational status, and occupation ($p<.001$).

**Conclusion:** Increased health literacy among people with chronic diseases positively influences rational use of medicines behaviours. In this context, the implementation and dissemination of education programs and counselling services aimed at improving health literacy in primary healthcare settings are recommended to promote rational use of medicines, support treatment adherence, and reduce preventable medication-related problems.


**Keywords:** Chronic disease, health literacy, primary healthcare.

## Introduction

Chronic diseases are commonly defined as conditions that are usually slow in progression, extend over many years, have a low probability of complete cure, and often lead to permanent loss of function. Socioeconomic, environmental, personal, and genetic factors jointly play a role in their onset and progression.[1] On a global scale, noncommunicable diseases accounted for at least 43 million deaths in 2021; this figure represents approximately three-quarters of all non-pandemic deaths worldwide.[2] In Türkiye, the prevalence of having at least one chronic disease is high among older adults (≥65 years).[3] When it comes to managing chronic diseases, health literacy plays a crucial role in determining an individual's ability to access, understand, evaluate, and apply health-related information.[4] In a nationwide study conducted by the General Directorate of Public Health Promotion of the Turkish Ministry of Health, approximately 70% of the population was reported to have substandard or suboptimal levels of health literacy.[5] Low health literacy adversely affects the use of preventive services, self-management of chronic conditions, and informed decision-making based on reliable information.[6,7] Advances in medicine have increased both the number and diversity of medications, while the need to ensure that treatments are delivered effectively, safely, and cost-effectively has brought the concept of Rational Use of Medicines to the forefront. Irrational use encompasses practices such as unnecessary prescribing, inappropriate dosage or duration, and poor management of multiple medication use (polypharmacy). These practices increase adverse effects and drug–drug interactions, fuel antimicrobial resistance, and impose an additional economic burden on health systems.[8,9] In Türkiye, rational use of medicines is also supported institutionally through national policies and educational materials.[10] The literature indicates a significant, positive association between health literacy and appropriate medication use: individuals with higher health literacy levels are more likely to use medicines with the correct indication, dose, and duration, to comprehend medication safety information, and to adhere to treatment regimens.[11,12] Therefore, strengthening health literacy, particularly among individuals with chronic diseases, constitutes a strategic lever for promoting rational use of medicines.[7,9] The objective of this study is to assess the correlation between health literacy levels and the judicious utilisation of medications among individuals afflicted with at least one chronic condition. The findings are expected to inform evidence for the design of targeted education and counselling programs in chronic disease management, as well as for policies that support the rational use of medicines.

## Materials and Methods

*Study Design and Population*

This study employed a descriptive, cross-sectional design. The target population consisted of all individuals with at least one chronic disease who presented to the [Bucak Central Family Medicine Units, District of Burdur] during the study period [15.07.2025-18.01.2026].

The sample size was determined a priori based on estimation of a population proportion using a 95% confidence level and a 5% margin of error, consistent with commonly used sample size tables/formulas for cross-sectional surveys. Assuming the most conservative scenario (p = 0.500, q = 0.50) and Z = 1.96, the required sample size was calculated using:

$$n = \frac{Z^2\, p(1-p)}{d^2}$$

Where Z = 1.96, p = 0.500, and d = 0.05, yielding a minimum sample size of approximately 384, which was rounded up to 386 participants. Ultimately, 488 eligible participants were included. Data were collected through face-to-face personal interviews conducted by the researchers in the family medicine units. Prior to participation, all individuals were informed about the study, and written informed consent was obtained. The study procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Participants were eligible if they were aged ≥18 years, had at least one physician-diagnosed chronic disease, they had to be able to communicate in Turkish, could complete a face-to-face interview, and provide written informed consent. Individuals were excluded if they were unable to participate in the interview due to severe cognitive impairment or a condition limiting reliable communication, had an acute medical condition requiring urgent care at the time of recruitment, declined participation/consent, or provided incomplete responses to the main study measures.

*Data Collection Tool*

Study data were collected using an Individual Identification Form, the Health Literacy Scale, and the Rational Use of Medicines Scale, all of which were developed or selected based on a review of the relevant literature. Individual ıdentification form was developed by the researchers and includes descriptive characteristics of the participants such as age, sex, educational status, occupation, and place of residence. The Rational Use of Medicines Scale was developed by Demirtaş et al.[13] to assess rational use of medicines and consists of 21 items. Responses are scored as follows: “Yes”=2 points, “I don’t know”=1 point, and “No”=0 points. The lowest score

you can get is 34; individuals scoring 35 points or above are considered to have adequate knowledge regarding the rational use of medicines. The Cronbach's alpha reliability coefficient of the scale was reported as 0.78. The original version of the Health Literacy Scale was developed by Toçi, Bruzari, and Sørensen[14], and its Turkish validity and reliability study was conducted by Aras and Temel (2017).[15] The scale consists of 25 items and comprises four sub-dimensions: Access (5-25 points), Understanding (7-35 points), Appraisal (8-40 points), and Application (5-25 points). Scores for the total scale range from 25 to 125.

*Data Analyses*

Data were entered into the SPSS 22.0 statistical software package (IBM Corp., Armonk, NY, USA). It was used numbers, percentages, means and standard deviations to describe the data. Independent samples t-tests and one-way analysis of variance (ANOVA) were employed when the assumptions of parametric tests were met. When these assumptions were not met, the Mann–Whitney U test and Kruskal–Wallis test were used. The chi-square test was applied to compare categorical variables. To examine the independent association between health literacy and rational use of medicines, we conducted multivariable linear regression analyses with the Rational Use of Medicines (RUM) total score as the dependent variable. Health Literacy (HL) total score was entered as the main predictor (scaled per 10-point increase). Models were adjusted for age category (<40, 40–59, ≥60), gender, marital status, educational status, and occupation. Given the bounded nature of scale scores and potential heteroskedasticity, heteroskedasticity-robust (HC3) standard errors and 95% confidence intervals were reported. As a sensitivity analysis, binary logistic regression was performed using adequate RUM (RUM ≥35) as the outcome. For all analyses, a p-value of less than 0.05 was considered statistically significant.

*Ethical Considerations*

The Non-Interventional Clinical Research Ethics Committee of Burdur Mehmet Akif Ersoy University provided its ethical approval for the study (Meeting date: 05.02.2025; Meeting No: 2025/2; Decision No: GO 2025/1041). Follow the Helsinki Declaration ethical standards.

## Results

The study included 55.3% women and 44.7% men. The majority were married (77.2%), while 22.8% were single. In terms of age, 39.6% were between 40 and 60 years, and 33.8% were younger than 40 years. Regarding educational status, primary school graduates constituted the largest group (44.5%), followed by those with a university degree or higher (35.5%). With respect to occupation, 30.7% of the participants were civil servants and 28.7% were housewives (Table 1).

**Table 1.** Demographic characteristics of the participants

| Variables | *n* | *%* |
|---|---|---|
| **Educational status** | | |
| Primary school | 217 | 44.47 |
| Secondary school | 28 | 5.74 |
| High school | 70 | 14.34 |
| University or higher | 173 | 35.45 |
| **Gender** | | |
| Female | 270 | 55.33 |
| Male | 218 | 44.67 |
| **Occupation** | | |
| Housewife | 140 | 28.69 |
| Retired | 89 | 18.24 |
| Civil servant | 150 | 30.74 |
| Worker / Self-employed | 109 | 22.34 |
| **Marital status** | | |
| Married | 377 | 77.25 |
| Single | 111 | 22.75 |
| **Age** | | |
| < 40 years | 165 | 33.81 |
| 40–60 years | 193 | 39.55 |
| > 60 years | 130 | 26.64 |

The mean total score on the Rational Use of Medicines Scale was 35.89±5.38, indicating a moderate level of awareness regarding rational use of medicines. The mean total score on the Health Literacy Scale was 104.66±15.49, suggesting a high level of health literacy among the participants. Reliability analyses showed that Cronbach's alpha coefficients for the subscales of the Health Literacy Scale ranged from 0.78 to 0.95, indicating high internal consistency. The Cronbach's alpha coefficient calculated for the Rational Use of Medicines Scale was 0.79, which is considered acceptable (Table 2).

A strong, positive correlation was found between the Rational Use of Medicines Scale scores and Health Literacy Scale scores ($r=0.60$, $p<0.001$). This finding indicates that as health literacy increases, individuals' rational use of medicines behaviours also improve (Table 3).

**Table 2.** Descriptive statistics and reliability coefficients for continuous variables

| Variables | *M* | *SD* | $SE_M$ | Min | Max | Skewness | Kurtosis | α | Lower Bound | Upper Bound |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rational Use of Medicines Scale** | 35.89 | 5.38 | 0.24 | 20.00 | 42.00 | -0.87 | -0.24 | .95 | .94 | .95 |
| **Health Literacy Scale** | 104.66 | 15.49 | 0.70 | 63.00 | 125.00 | -0.60 | -0.35 | .89 | .88 | .90 |
| **Understanding** | 27.87 | 5.65 | 0.26 | 13.00 | 35.00 | -0.53 | -0.42 | .88 | .87 | .89 |
| **Appraisal** | 33.68 | 5.49 | 0.25 | 22.00 | 40.00 | -0.55 | -0.97 | .91 | .90 | .92 |
| **Access** | 21.13 | 3.81 | 0.17 | 8.00 | 25.00 | -0.96 | 0.47 | .78 | .75 | .80 |
| **Application** | 21.98 | 2.82 | 0.13 | 13.00 | 25.00 | -1.07 | 0.84 | .79 | .77 | .81 |

*M = mean; SD = standard deviation; SE<sub>M</sub> = standard error of the mean; Min = minimum; Max = maximum; skewness = skewness coefficient; kurtosis = kurtosis coefficient; α = Cronbach's alpha; lower bound = lower bound of the 95% confidence interval for α; upper bound = upper bound of the 95% confidence interval for α.

**Table 3.** Pearson correlation between rational use of medicines and health literacy scale scores

| Combination | *r* | 95.00% CI | *n* | *p* |
|---|---|---|---|---|
| **Rational Use of Medicines Scale – Health Literacy Scale** | .60 | [.54, .65] | 488 | <0.001 |

*r = Pearson correlation coefficient; 95.00% CI = 95% confidence interval; n = sample size; p = p value (level of significance).

Table 4 presents comparisons of the Rational Use of Medicines (RUM) and Health Literacy (HL) total scores across sociodemographic groups. For RUM, females had significantly higher scores than males (37.08±5.26 vs 34.42±5.19; t(486)=5.58, p<0.001, d=0.51). Single participants also had higher RUM scores compared with married participants (37.35±4.35 vs 35.46±5.58; Welch t(226.8)=-3.75, p<0.001, d=-0.35). RUM scores differed significantly by occupation (F(3,484)=41.37, p<0.001, $\eta p^2$=0.20), age group (F(2,485)=69.14, p<0.001, $\eta p^2$=0.22), and educational status (F(3,484)=49.88, p<0.001, $\eta p^2$=0.24). The highest RUM mean was observed among participants with university education or higher (39.21±2.73) and those aged <40 years (38.52±3.08), whereas the lowest mean was observed in the ≥60 age group (32.00±6.44) and among retired participants (32.43±5.90).

**Table 4.** Comparison of rational use of medicines and health literacy scale scores by sociodemographic characteristics

| | | Rational Use of Medicines Scale (RUM total score) | | | | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Category** | **n** | **Mean** | **SD** | **Test (df)** | **p** | **Effect size** |
| **Sex** | Female | 270 | 37.08 | 5.26 | t(486)=5.58 | <0.001 | d=0.51 |
| | Male | 218 | 34.42 | 5.19 | | | |
| **Marital status** | Married | 377 | 35.46 | 5.58 | t(226.8)=-3.75 | <0.001 | d=-0.35 |
| | Single | 111 | 37.35 | 4.35 | | | |
| **Occupation** | Housewife | 140 | 34.30 | 5.81 | F(3,484)=41.37 | <0.001 | $\eta p^2$=0.20 |
| | Retired | 89 | 32.43 | 5.90 | | | |
| | Civil servant | 150 | 38.96 | 2.85 | | | |
| | Worker/Self-employed | 109 | 36.54 | 4.59 | | | |
| **Age group** | <40 | 165 | 38.52 | 3.08 | F(2,485)=69.14 | <0.001 | $\eta p^2$=0.22 |
| | 40–59 | 193 | 36.27 | 4.61 | | | |
| | ≥60 | 130 | 32.00 | 6.44 | | | |
| **Educational status** | Primary school | 217 | 33.81 | 5.85 | F(3,484)=49.88 | <0.001 | $\eta p^2$=0.24 |
| | Middle school | 28 | 31.75 | 5.41 | | | |
| | High school | 70 | 35.80 | 4.39 | | | |
| | University or higher | 173 | 39.21 | 2.73 | | | |
| | | **Health Literacy Scale (HL total score)** | | | | | |
| **Variable** | **Category** | **n** | **Mean** | **SD** | **Test (df)** | **p** | **Effect size** |
| **Sex** | Female | 270 | 105.11 | 16.20 | t(486)=0.72 | 0.475 | d=0.07 |
| | Male | 218 | 104.11 | 14.58 | | | |
| **Marital status** | Married | 377 | 104.00 | 15.60 | t(486)=-1.74 | 0.082 | d=-0.19 |
| | Single | 111 | 106.91 | 14.97 | | | |
| **Occupation** | Housewife | 140 | 96.10 | 15.31 | F(3,484)=45.61 | <0.001 | $\eta p^2$=0.22 |
| | Retired | 89 | 101.93 | 17.49 | | | |
| | Civil servant | 150 | 114.60 | 10.64 | | | |
| | Worker/Self-employed | 109 | 104.22 | 11.68 | | | |
| **Age group** | <40 | 165 | 110.56 | 11.56 | F(2,485)=41.27 | <0.001 | $\eta p^2$=0.15 |
| | 40–59 | 193 | 105.82 | 11.86 | | | |
| | ≥60 | 130 | 95.46 | 19.87 | | | |
| **Educational status** | Primary school | 217 | 95.94 | 15.38 | F(3,484)=70.51 | <0.001 | $\eta p^2$=0.30 |
| | Middle school | 28 | 104.00 | 7.24 | | | |
| | High school | 70 | 106.20 | 10.75 | | | |
| | University or higher | 173 | 115.10 | 11.02 | | | |

*M = mean; SD = standard deviation; t = t-test statistic; p = p value (level of significance); d = Cohen's d (effect size); SS = sum of squares; df = degrees of freedom; F = ANOVA F statistic; $\eta p^2$ = partial eta squared (effect size).

For HL, there were no statistically significant differences by sex (105.11±16.20 vs 104.11±14.58; t(486)=0.72, p=0.475, d=0.07) or marital status (104.00±15.60 vs 106.91±14.97; t(486)=-1.74, p=0.082, d=-0.19). However, HL scores differed significantly by occupation (F(3,484)=45.61, p<0.001, $\eta p^2$=0.22), age group (F(2,485)=41.27, p<0.001, $\eta p^2$=0.15), and educational status (F(3,484)=70.51, p<0.001, $\eta p^2$=0.30). Participants with university education or higher had the highest HL scores (115.10±11.02), while the ≥60 age group had the lowest HL mean (95.46±19.87).

In the multivariable linear regression model, higher health literacy was independently associated with higher rational use of medicines. Specifically, each 10-point increase in HL total score was associated with a 1.44-point increase in the RUM total score (B=1.435, SE=0.154, 95% CI 1.133–1.737, p<0.001). Compared with females, males had significantly lower RUM scores (B=−2.853, 95% CI −3.697 to −2.008, p<0.001). Single participants had slightly lower RUM scores than married participants after adjustment (B=−0.862, 95% CI −1.666 to −0.058, p=0.036). Relative to primary education, secondary education was associated with lower RUM scores (B=−2.973, p<0.001), whereas university education or higher was associated with higher RUM scores (B=1.783, p=0.003); high school education was not significant (p=0.211). Regarding occupation, being a worker/self-employed was associated with higher RUM scores compared with housewives (B=1.586, p=0.014), while being retired or a civil servant was not significant (p>0.050). Participants aged ≥60 years had significantly lower RUM scores than those aged 40–59 years (B=−2.720, p<0.001), whereas the <40 age group did not differ significantly (p=0.172). Overall, the model explained 52.2% of the variance in RUM scores ($R^2$=0.522; adjusted $R^2$=0.511) (Table 5).

**Table 5.** Multivariable linear regression model predicting Rational Use of Medicines (RUM) total score

| Predictor | B | SE | CI_low | CI_high | p |
|---|---|---|---|---|---|
| HL total (per 10 points) | 1.435 | 0.154 | 1.133 | 1.737 | <0.001 |
| Gender: male (ref=female) | -2.853 | 0.430 | -3.697 | -2.008 | <0.001 |
| Marital status: single (ref=married) | -0.862 | 0.409 | -1.666 | -0.058 | 0.035 |
| Education: secondary (ref=primary) | -2.973 | 0.721 | -4.390 | -1.557 | <0.001 |
| Education: high school (ref=primary) | -0.809 | 0.645 | -2.077 | 0.459 | 0.210 |
| Education: university+ (ref=primary) | 1.783 | 0.594 | 0.616 | 2.951 | 0.002 |
| Occupation: retired (ref=housewife) | 0.493 | 0.838 | -1.154 | 2.140 | 0.556 |
| Occupation: civil servant (ref=housewife) | 0.302 | 0.721 | -1.115 | 1.720 | 0.675 |
| Occupation: worker/self-employed (ref=housewife) | 1.586 | 0.641 | 0.327 | 2.846 | 0.013 |
| Age: <40 (ref=40–59) | 0.618 | 0.452 | -0.270 | 1.505 | 0.172 |
| Age: ≥60 (ref=40–59) | -2.720 | 0.750 | -4.193 | -1.246 | <0.001 |
| **Model fit** | $R^2$=0.522; Adjusted $R^2$=0.511; n=488 | | | | |

*B: unstandardized coefficient; SE: standard error; CI: 95% confidence interval. HL was scaled per 10-point increase. Reference categories: female (gender), married (marital status), primary (education), housewife (occupation), and age 40–59 years (age group).

## Discussion

In this study, we examined the relationship between health literacy and rational use of medicines among individuals with chronic diseases and evaluated differences according to sociodemographic variables. Our findings indicate a positive and strong association between rational use of medicines and health literacy (r=0.60, $p$<0.001). This result is consistent with recent evidence suggesting that higher health literacy supports more appropriate/rational use of medicines. For example, a systematic review assessing the relationship between health literacy and medication adherence in adults with chronic disease demonstrated that low health literacy is significantly associated with poor adherence.[16] Similarly, a systematic review conducted in 2025 among adults with type 2 diabetes highlighted the key role of health literacy in determining medication adherence.[17] A recent meta-analysis from Türkiye also reported a moderate positive association between health literacy and rational use of medicines (effect sizes ≈0.21-0.62), which is in line with the correlation observed in our sample (r=0.60).[18] Importantly, this association remained significant after adjustment for sociodemographic factors in the multivariable model, suggesting that health literacy is independently related to rational use of medicines in this population.

In our study, health literacy levels were high, whereas awareness of the rational use of medicines was at a moderate level. This pattern suggests that although individuals have an improved capacity to access and understand information, they may have trouble translating this knowledge into rational medication behaviours in practice. This "knowledge–behavior gap," which is reflected in clinical settings, is one of the key targets of the World Health Organisation's "Medication Without Harm" global patient safety challenge. To reduce serious and preventable medication-related harm, WHO recommends improvements at the individual, team, and system levels across prescribing, administration, and monitoring processes. In particular, the technical report on polypharmacy emphasises the importance of regular medication review in high-risk groups, patient education, and team-based approaches.[9] When considered together with our findings, this framework supports the potential clinical value of structured education and counselling programs that both enhance health literacy and promote rational use of medicines.

The significant differences observed in our study according to age and educational level are also consistent with the literature. We found that rational use of medicines scores were significantly lower among individuals aged ≥60 years, whereas both rational use of medicines and health literacy scores were markedly higher among those with a university degree or higher. Notably, education showed a heterogeneous pattern in adjusted analyses, indicating that differences in rational medicine use may not increase linearly across all education categories. Evidence from studies among patients with hypertension has shown that health literacy tends to decline with advancing age,[19] while research in individuals with obesity has demonstrated a strong positive effect of educational attainment on health literacy,[20] supporting our findings. Furthermore, a study that

identified a positive relationship between eHealth literacy and medication adherence indicated that digital competencies may improve adherence behaviours, particularly in the context of chronic disease management.[21] Taken together, these findings suggest that, in older adults, cognitive, auditory, and visual limitations, as well as the complexity of managing multiple medications, should be specifically addressed; in individuals with lower educational levels, barriers in accessing and critically appraising evidence-based information need to be targeted.

Beyond age and education, sex and marital status were also associated with the rational use of medicines. In the adjusted model, men had lower RUM scores than women, and single participants had slightly lower RUM scores than married participants, whereas differences in health literacy by sex or marital status were not evident. These patterns suggest that factors beyond health literacy (e.g., medication experiences, roles in medication management, or health service interactions) may contribute to rational medicine use. Given national reports indicating that health literacy levels in Türkiye are heavily concentrated in inadequate or problematic categories,5 the need for community-based interventions has long been emphasised. Findings from the European HLS-EU project and its conceptual frameworks also demonstrate that health literacy is closely linked to social determinants such as education, income, and employment.[4] In this context, our results underline the importance of prioritising groups with lower health literacy scores, such as housewives and individuals with lower educational attainment, through multicomponent strategies. This is further supported by the adjusted findings showing occupational differences in rational medicine use, underscoring the need for tailored interventions in primary care. These may include simplified written materials, visual and audio educational content, guided use of eHealth tools, and brief, structured educational interventions delivered in primary care settings.

In conclusion, our findings show that individuals in this sample generally have high levels of health literacy but only moderate awareness of the rational use of medicines. Rational use of medicines was significantly and positively associated with health literacy in this sample. Therefore, interventions aiming to improve health literacy among individuals with chronic diseases may be a promising strategy to support the rational use of medicines.

In line with this, we recommend that healthcare professionals, particularly nurses and physicians working in family medicine units, regularly assess patients' medication use habits and implement education and counselling programs designed to strengthen health literacy. In addition, the use of digital health tools and simplified educational materials may enhance awareness of medication safety, especially among older adults and individuals with lower educational levels.

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**Ethical Considerations:** The Non-Interventional Clinical Research Ethics Committee of Burdur Mehmet Akif Ersoy University provided its ethical approval for the study (Meeting date: 05.02.2025; Meeting No: 2025/2; Decision No: GO 2025/1041). Follow the Helsinki Declaration ethical standards.

**Conflict of Interest:** The authors declare no conflict of interest.

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Research Article

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# UNEXPLAINED FATIGUE IN THE HEALTHY POPULATION: THE ROLE OF DEPRESSION, SLEEP, AND SOCIAL FACTORS

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## Abstract

**Objectives:** Fatigue is characterised as a feeling of exhaustion that arises with a reduction in the ability to engage in physical or mental activities. This study aims to examine the root causes of fatigue symptoms and associated demographic characteristics among persons devoid of any underlying medical disorders.

**Materials and Methods:** The study included 125 patients who visited the outpatient neurology clinic reporting fatigue. Data was collected using the Chalder Fatigue Scale (CFS), the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale, the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI).

**Results:** The mean age of the patients was 46.01±12.10 years, with 67.2% (n=84) being female. The prevalence of individuals who were married (p=0.002), employed (p=0.004), and possessed a university degree (p=0.033) was greater among women compared to men. Elevated BDI scores were (OR: 1.192, 95% CI: 1.057–1.337, p=0.003) and PSQI scores (OR: 1.782, 95% CI: 1.376–2.192, p<0.001) significantly associated with higher fatigue severity. The CFS ratings were significantly elevated in individuals with a university degree relative to those with primary education (OR: 3.032, 95% CI: 1.099–8.122, p=0.031). Unemployment was associated with a markedly reduced probability of experiencing fatigue (OR: 0.083, 95% CI: 0.032-0.232, p<0.001).

**Conclusion:** Our study demonstrated that elevated educational attainment, unemployment, compromised sleep quality, and heightened depression were associated with fatigue symptoms. The data demonstrate that weariness is associated not only with physiological aspects but also highly impacted by psychological and social factors.


**Keywords:** Fatigue, depression, sleep disorder, anxiety.

## Introduction

Fatigue is characterised as a feeling of exhaustion resulting from diminished physical or mental activity capacity. Fatigue is a significant symptom linked to various chronic health conditions and can adversely affect quality of life.[1] The prevalence in European countries ranges from 20% to 60%, contingent upon the assessment methodologies and the age demographics examined.[2,3] Commonly observed in primary care, weariness detrimentally influences patients' quality of life and diminishes productivity, hence significantly affecting national economies.

Fatigue has been linked to various causes, including physical, psychological, and environmental issues such as lifestyle and occupational circumstances. Studies have shown that sleep disruptions, psychosocial stress, depression, and respiratory illnesses are prevalent causes of chronic fatigue.[4] In contemporary societies, shifts in job and family obligations, coupled with a rise in the incidence of illnesses like metabolic syndrome, anxiety, and depression, have resulted in detrimental modifications to the requisite quantity of sleep for optimal physiological functioning.[5] Furthermore, the wholly subjective nature of fatigue and the absence of definitive diagnostic criteria have compelled neurologists, who often observe this symptom in clinical settings, to investigate its underlying causes. Nonetheless, whereas the majority of current research has concentrated on particular disorders, our study sought to examine the fundamental causes and demographic attributes of fatigue symptoms among persons devoid of any recognised medical conditions.

## Materials and Methods

*Study design and participants*

This prospective study was approved by the Ankara City Hospital Ethics Committee on December 10, 2022 (Protocol No: E2-22-2556), and all procedures adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent. One hundred twenty-five patients presenting with fatigue at the outpatient neurology clinic from November 2022 to March 2025 were included in the study. Patients exhibiting fatigue and having a history of diabetes mellitus, hypertension, rheumatologic diseases, chronic kidney disease, oncologic conditions, chemotherapy, immunologic disorders, thyroid dysfunction, heart disease, anaemia, recent infections, or prior medication use were excluded from the study. Furthermore, pregnant women, individuals below 18 years of age, and those who opted out of participation were excluded from the study. Data on age, sex, marital status, occupational status, and educational attainment were collected for all participants.

*Data collection and questionnaires*

For data collection, questionnaires were distributed to participants who consented after being fully informed about the study. Questionnaires were collected on the same day they were completed.

This study utilised the Chalder Fatigue Scale (CFS) to evaluate fatigue levels. The CFS comprises 11 items that assess physical and mental fatigue. Items are evaluated using a 4-point scale that ranges from asymptomatic to maximal symptomatology. Likert scoring (0–3) was utilised, resulting in total scores from 0 to 33; elevated scores reflect increased severity of fatigue.[6]

The Pittsburgh Sleep Quality Index (PSQI) was utilised to assess sleep quality. The PSQI consists of seven components that evaluate sleep disturbances and overall sleep quality during the preceding month. The scoring for each item ranges from 0 to 3, resulting in a cumulative score that spans from 0 to 21. Scores exceeding 5 signify inadequate sleep quality.[7]

The overall degree of daytime sleepiness was evaluated utilising the Epworth Sleepiness Scale (ESS). The ESS is an 8-item tool designed to assess the probability of dozing off or falling asleep during routine activities, utilising a 4-point Likert-type scale (0–3) for scoring. Total scores vary between 0 and 24, with scores exceeding 10 signifying excessive daytime sleepiness.[8]

The Beck Depression Inventory (BDI) is a self-report tool intended to evaluate cognitive, emotional, and motivational symptoms related to depression. The instrument comprises 21 items, each rated on a 0–3 scale, with the cumulative score reflecting the severity of depressive symptoms.[9] The Beck Anxiety Inventory (BAI) is a self-report questionnaire consisting of 21 items designed to assess the severity of anxiety symptoms, particularly somatic and cognitive components of anxiety. Each item is scored on a 4-point Likert scale ranging from 0 to 3, with higher total scores indicating greater anxiety severity. The BAI has been widely validated and is commonly used in both clinical and research settings. [10]

*Statistical Analysis*

In this study, data analysis was performed using IBM SPSS Statistics version 25.0. Descriptive statistics are presented as numbers (n) and percentages (%) for categorical variables, and as mean ± standard deviation for continuous variables. For comparisons between groups, the Independent Samples t-test was used for continuous variables, and the Chi-square test was applied for categorical variables. To identify the factors affecting the CFS, multivariable logistic regression analysis was conducted. Variables included in the multivariable logistic regression model were selected based on clinical relevance and prior evidence from the literature. In addition, variables showing an association with fatigue at a significance level of $p < 0.10$ in

univariate analyses were entered into the multivariable model. The logistic regression analysis was performed using the enter method. For continuous variables found to be significant (PSQI and BDI), receiver operating characteristic (ROC) curves and the area under the curve (AUC) were utilised. A p-value of <0.05 was considered statistically significant.

Although this study was prospective, it was designed as an exploratory, observational study without an interventional hypothesis. Therefore, no a priori sample size calculation was performed. All consecutive patients who met the inclusion criteria during the study period were enrolled.

To assess the adequacy of the final sample size, receiver operating characteristic (ROC) curve analysis was performed for the main predictor variables. The area under the curve (AUC) values were reported together with 95% confidence intervals, and statistical significance was tested against the null hypothesis of AUC = 0.50.

## Results

Out of 214 patients presenting to the neurology outpatient clinic with fatigue complaints, 125 were included in the study. Figure 1 illustrates the enrollment process in detail.

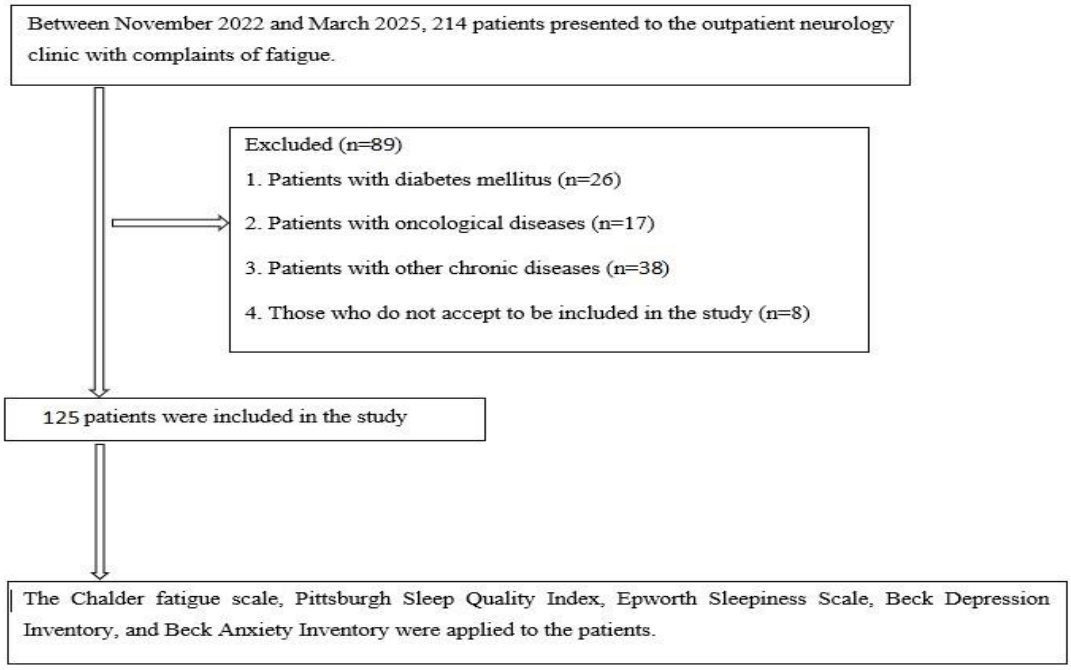


**Figure 1.** Flow chart of patients included in the study

The demographic characteristics and questionnaire scores of the patients are listed in Table 1. The mean age of the patients was 46.01 ± 12.10 years, and 67.2% (n=84) were female. Of the patients, 64% (n=80) were married, and 50.4% (n=63) had children. Regarding employment status, 48.8% (n=61) were employed, 38.4% (n=48) were unemployed, and 12.8% (n=16) were students. In terms of educational level, 24% (n=30) had a primary school education, 43.2% (n=54) had completed high school, and 32.8% (n=41) held a university degree. The proportion of married, employed, and university-educated patients was higher among women than men (p=0.002, p=0.004, p=0.033). The mean scores on the scales were as follows: Chalder Fatigue Scale 21.21 ± 4.16, Pittsburgh Sleep Quality Index 8.32 ± 2.88, Epworth Sleepiness Scale 9.20 ± 3.55, Beck Depression Inventory 17.43 ± 6.21, and Beck Anxiety Inventory 15.90 ± 5.06. Total scores on all scales were significantly higher in women than in men (p<0.05) (Table 1).

**Table 1.** Demographic characteristics of patients and questionnaire results

| | **Male** (n=41) | **Female** (n=84) | **Total** (n=125) | **p** |
|---|---|---|---|---|
| **Age(Mean±SD)** | 48.39 ± 11.88 | 44.85 ± 12.10 | 46.01 ± 12.10 | 0.124 |
| **Marital Status** | | | | |
| Married | 18 (44%) | 62 (74%) | 80 (64%) | 0.002 |
| Single | 23 (56%) | 22 (26%) | 45 (36%) | |
| **Children** | | | | |
| Yes | 30 (73.2%) | 33 (39.3%) | 63 (50.4%) | 0.449 |
| No | 11 (26.8%) | 51 (60.7%) | 62 (49.6%) | |
| **Employment Status** | | | | |
| Employed | 14 (34.1%) | 47 (55.9%) | 61 (48.8%) | 0.004 |
| Unemployed | 22 (53.7%) | 26 (31.0%) | 48 (38.4%) | |
| Student | 5 (12.2%) | 11 (13.1%) | 16 (12.8%) | |
| **Education Level** | | | | |
| Primary school | 12 (29.2%) | 18 (21.4%) | 30 (24%) | 0.033 |
| High school | 22 (53.7%) | 32 (38.1%) | 54 (43.2%) | |
| University | 7 (17.1%) | 34 (40.5%) | 41 (32.8%) | |
| **CFS** | 18.95±3.89 | 22.31±3.85 | 21.21±4.16 | < 0.001 |
| **PSQI** | 7.00±2.77 | 8.96±2.73 | 8.32±2.88 | < 0.001 |
| **Epworth SS** | 7.95±2.86 | 9.81±3.71 | 9.20±3.55 | 0.002 |
| **BDI** | 14.59 ±5.87 | 18.82 ±5.92 | 17.43 ±6.21 | < 0.001 |
| **BAI** | 13.41±4.95 | 17.12±4.67 | 15.90±5.06 | < 0.001 |

CFS: Chalder Fatigue Scale, PSQI: Pittsburgh Sleep Quality Index, Epworth SS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory

Factors associated with fatigue were evaluated using a multivariate logistic regression model. Increased BDI scores were significantly associated with higher fatigue scores (OR: 1.192, 95% CI: 1.057–1.337, p=0.003). Similarly, higher PSQI scores were significantly associated with higher fatigue scores (OR: 1.782, 95% CI: 1.376–2.192, p<0.001). University-educated individuals had higher CFS scores compared to those with primary education (OR: 3.032, 95% CI: 1.099–8.122, p=0.031), while unemployed individuals were significantly less likely to report fatigue (OR: 0.083, 95% CI: 0.032-0.232, p<0.001). (Table 2)

**Table 2.** Multivariate logistic regression analysis of factors associated with fatigue

| **Variables** | β | SE | **OR (95% CI)** | p |
|---|---|---|---|---|
| **Age** | 0.016 | 0.014 | 1.021 (0.992-1.055) | 0.234 |
| **Gender** (Male) | 0.637 | 0.401 | 1.588 (0.722-3.492) | 0.115 |
| **BDI** | 0.172 | 0.06 | 1.192 (1.057-1.337) | **0.003** |
| **BAI** | -0.036 | 0.066 | 0.965 (0.848–1.098) | 0.584 |
| **PSQI** | 0.577 | 0.101 | 1.782 (1.376-2.192) | **<0.001** |
| **Epworth SS** | 0.004 | 0.069 | 1.002 (0.871-1.142) | 0.953 |
| **Education** (University) | 1.112 | 0.510 | 3.032 (1.099-8.122) | **0.031** |
| **Employment** (Unemployed) | -2.558 | 0.549 | 0.083 (0.032-0.232) | **<0.001** |
| **Children** (Yes) | 0.276 | 0.503 | 1.324 (0.492-3.582) | 0.584 |
| **Marital Status**(Married) | -0.326 | 0.540 | 0.722 (0.243-2.112) | 0.547 |

Nagelkerke $R^2$ = 0.826, SE: standard error, OR: Odds Ratio, CI: confidence interval, PSQI: Pittsburgh Sleep Quality Index, Epworth SS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory

ROC curve analysis was performed to identify cut-off values for the continuous variables that were significant in the logistic regression (PSQI and BDI). The PSQI cut-off value was 8 (specificity: 86%, sensitivity: 86%, AUC: 0.911), and the BDI cut-off value was 17 (specificity: 95%, sensitivity: 77%, AUC: 0.865). (Figure 2)

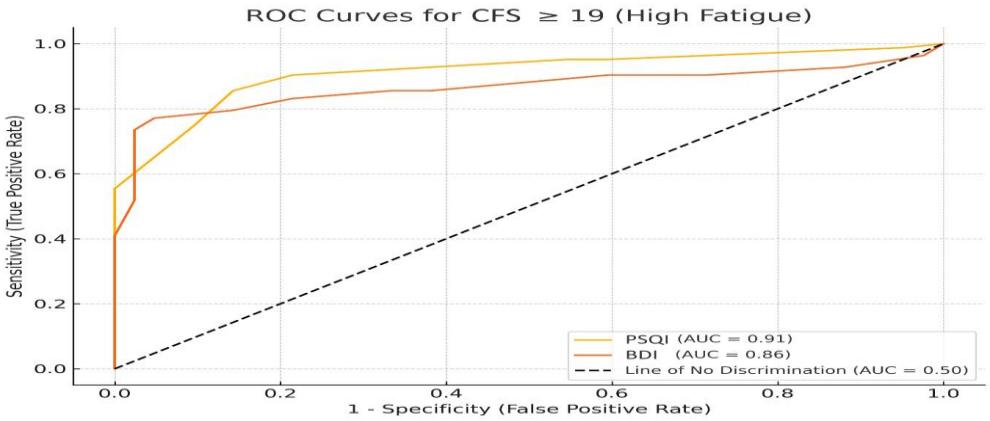


**Figure 2.** ROC curve analysis for Chalder Fatigue Scale

## Discussion

In this study, we investigated the demographic and psychosocial factors associated with fatigue, a symptom frequently encountered in clinical practice, among individuals without a formal medical diagnosis. Our findings demonstrate that higher educational level, unemployment, impaired sleep quality, and increased depression are associated with fatigue symptoms. These results underscore that fatigue is not only related to physiological factors but is also significantly influenced by psychological and social variables.

The majority of individuals presenting with fatigue symptoms were women, and these women were more likely to be married, employed, and highly educated. In a recent nationwide, population-based cross-sectional survey conducted by Cruickshank et al., female sex and lower educational level were associated with a greater risk of fatigue.[11] Conversely, in another study, Knoers et al. reported that fatigue was more prevalent among employed, highly educated women.[12] The elevated fatigue scores observed in working individuals may reflect the cumulative impact of occupational and daily responsibilities, which can deplete an individual's physical and mental resources. The significantly lower fatigue scores in unemployed individuals support this hypothesis. Furthermore, we propose that high educational attainment may contribute to increased fatigue due to heightened expectations and performance anxiety in both occupational and personal domains. Consistent with these findings, we observed that women had significantly higher scores across all questionnaires. We suggest that multiple factors could account for this observation, including higher rates of depression, anxiety, and sleep disturbances among women, as well as differences in healthcare-seeking behaviour and symptom reporting. Additionally, biological, hormonal, and social role differences may also contribute to more pronounced experiences of fatigue in women. The dual burden of managing domestic responsibilities alongside professional commitments can limit time for rest and recuperation, potentially predisposing women to chronic fatigue. Our findings, including higher depression, anxiety, and sleep disturbance scores among female participants, support this multidimensional interplay.

In our study, we observed a strong positive correlation between PSQI and CFS scores and determined an optimal PSQI cut-off value of 8 via ROC analysis. These results suggest that impaired sleep quality is a substantial contributing factor in the emergence of fatigue symptoms. In a study by Ju Kim et al., insomnia severity and daytime sleepiness were found to be closely related to fatigue severity. Their findings indicated that poor sleep quality has considerable effects on daily energy levels and cognitive performance, and that managing insomnia or depression could alleviate fatigue.[13] Prior research has also shown that declining sleep quality and increased fatigue with ageing are associated with reduced quality of life and mortality.[14,15] Moreover, Christie et al. demonstrated that improving sleep in older adults can reduce self-reported fatigue independently of increased physical activity.[16]

Our study revealed a significant correlation between increased fatigue scores and elevated levels of depression. ROC analysis determined a cut-off value of 17 for the Beck Depression Inventory. Depression affects fatigue not only through mood alterations but also via various mechanisms, such as diminished motivation, social withdrawal, and disrupted sleep patterns. A recent population-based study demonstrated an association between depression and both fatigue symptoms and daytime sleepiness.[17] Fatigue, influenced by its emotional and cognitive dimensions, may be linked to various psychiatric and physical diagnoses.[18,19] Research indicates that individuals with medically unexplained fatigue have an approximately 11-fold increased likelihood of being diagnosed with depression relative to those without such fatigue.[20] Our findings align with existing literature, indicating that individuals exhibiting fatigue symptoms report higher levels of depression than the general population.[21] Fatigue must be examined from both medical and psychosocial viewpoints. Mood disturbances, social support levels, coping mechanisms for stress, and lifestyle habits can all affect the severity of fatigue symptoms. The findings of our study indicate a significant correlation among depression, sleep quality, and fatigue, underscoring the importance of a comprehensive evaluation of these symptoms.

Nonetheless, certain limitations exist. The limited sample size and single-centre design may constrain the generalizability of the findings. Furthermore, considering that fatigue is a subjective symptom significantly shaped by individual perception, the objective measurement of this variability is often impractical.

In conclusion, this study indicates that elevated educational attainment, unemployment, poor sleep quality, and heightened depression are associated with fatigue symptoms. The findings suggest that fatigue is related not only to physiological factors but also to psychological and social factors. Future studies with larger sample sizes, preferably multicenter and longitudinal in design, are warranted to provide deeper insights into the mechanisms underlying fatigue symptoms and to improve diagnostic and therapeutic approaches in clinical practice.

**Ethical Considerations:** The study was approved by Ankara City Hospital Ethics Committee on 12/10/2022, protocol number E2-22-2556, and all procedures were carried out in accordance with the principles of the Declaration of Helsinki.

**Conflict of Interest:** The authors declare no conflict of interest.

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# HEART RATE VARIABILITY AS A MARKER OF CARDIAC AUTONOMIC NEUROPATHY AND AUTONOMIC DYSFUNCTION IN PREDIABETIC PATIENTS: A RETROSPECTIVE STUDY

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## Abstract

**Objectives:** Heart rate variability has been associated with autonomic neuropathy, which is seen in diabetes. Cardiac autonomic neuropathy is found to be related to a poor prognosis in diabetic patients. It is thought that neuropathy that develops in diabetic patients begins in the early stages. We aimed to assess heart rate variability (HRV) in prediabetic patients to explore whether autonomic changes may begin during the prediabetes stage.

**Materials and Methods:** This retrospective study included prediabetic patients who underwent 24-hour Holter ECG monitoring. Patients were identified based on fasting plasma glucose (FPG) and HbA1c values extracted from medical records. Prediabetes was defined as HbA1c 5.7–6.4% and fasting plasma glucose 100–126 mg/dL. Patients with thyroid dysfunction, overt diabetes, arrhythmias or those using drugs affecting heart rate were excluded. HRV parameters, including SDNN, SDANN, rMSSD, pNN50, triangular index, and frequency-domain measures (LF, HF, VLF, LF/HF), were analysed.

**Results:** Fifty participants were included (25 prediabetic, 25 controls). The groups were similar in age and sex. All HRV parameters were lower in prediabetic patients compared to controls. Time-domain measures SDANN, rMSSD, pNN50, and triangular index and frequency-domain measures HF, VLF, and LF/HF ratio were significantly reduced ($p < 0.05$). Effect sizes and 95% confidence intervals were reported, and sensitivity analyses adjusted for age and sex confirmed findings.

**Conclusion:** HRV is reduced in prediabetic patients, consistent with early autonomic dysfunction. These findings suggest that cardiac autonomic neuropathy may begin in prediabetic patients. All HRV parameters were lower than those of the control group and can serve as non-invasive indicators of early autonomic dysfunction and cardiac autonomic neuropathy.

**Keywords:** Prediabetes, heart rate, autonomic neuropathy.

## Introduction

Cardiac autonomic neuropathy has been associated with increased morbidity and mortality in diabetic patients.[1] Neuropathy in diabetic patients is thought to begin in the early stages; studies suggest that autonomic dysfunction may begin before the diagnosis of diabetes, during the prediabetic stage.[1] Heart Rate Variability Indicates Early Autonomic Dysfunction in Prediabetic Patients. Investigation of heart rate variability in prediabetic patients may indicate that autonomic neuropathic changes begin during the prediabetic phase.

Preventing the diagnosis of diabetes at the prediabetes stage is the most beneficial method to treat the complications that may arise. Macrovascular and microvascular complications of diabetes directly affect the cardiovascular system, and most of the diabetes deaths are cardiovascular-related. Early recognition may be cost-effective and guide clinicians and at-risk individuals in implementing timely lifestyle interventions. Cardiovascular autonomic neuropathy can be diagnosed noninvasively by considering the heart rate variability. Diabetic cardiovascular autonomic neuropathy, which is not studied much in clinical practice and can be diagnosed early due to clinicians paying more attention to other macrovascular complications and microvascular complications of diabetes, is diagnosed late.

The definition of 'prediabetes' has been accepted by the ADA for conditions that do not have high blood sugar to meet the diagnosis of diabetes, but are at a level that cannot be considered normal.[2] (Table 1)

**Table 1**. Criteria for diagnosing diabetes mellitus and other glucose metabolism disorders[1]

| | **Normal** | **Prediabetes** | **Diabetes** |
|---|---|---|---|
| **Fasting Plasma Glucose(FPG)** | <100 mg/dL | 100-125 mg/dL | ≥ 126 mg/dL |
| **2-hr OGTT (75 g glucose)** | <140 mg/dL | 140-199 mg/dL | ≥ 200 mg/dL |
| **HbA1c** | <5.7% | 5.7-6.4% | ≥ 6.5% |
| **Random Plasma Glucose** | - | - | ≥ 200 mg/dl + symptoms |

FPG: Fasting Plasma Glucose, OGTT: Oral Glucose Tolerance Test, HbA1c: Hemoglobin A1c

In the light of the new diagnostic criteria, the presence of fasting plasma glucose in the range of 100-125 mg/dL' impaired fasting glucose [IFG]' and/or oral glucose tolerance test (OGTT 75 g) 2nd-hour value in the range of 140-199 mg/dL 'impaired glucose tolerance [IGT]' and/or HbA1c value defined as 5.7-6.4% defines the cases where both diabetes risk and complications and cardiovascular disease risk increase.[3]

The definition of 'prediabetes' is used for values that do not fully meet the diagnostic criteria for diabetes, but whose plasma glucose levels are higher than normal., includes impaired fasting glucose (IFG), impaired glucoe tolerance (IGT) which were previously referred to as 'Borderline Diabetes' or 'Latent Diabetes', are now accepted as 'Prediabetes'.

The risk of developing diabetes mellitus in pre-diabetic individuals increases up to 4-9% in those with IFG or IGT, and up to 19% in those with both.[4]

According to the data described in TURDEP-II, the prevalence of diabetes in our country was found to be 13.7%, the prevalence of IGT was found to be 7.9%, and the prevalence of IFG was found to be 14.7%.[5] In the pathophysiology of the transition from prediabetes to diabetes, insulin resistance and beta-cell dysfunction are prevalent, and it is accepted that this mechanism starts at the prediabetes stage before the development of diabetes.[6]

According to research findings, prediabetes is associated with macrovascular and especially cardiovascular complications, and the cardiovascular risk is further increased in people with high plasma glucose at the second hour, and in people with IGT and IFG. [7] It has been revealed that fasting blood sugar, IFG, IGT and prediabetic HbA1c at prediabetic levels are directly associated with cardiovascular mortality and complications and are independent risk factors.[8, 9, 10]

It has also been shown that complications such as nephropathy, retinopathy and neuropathy seen in diabetes can also be seen in prediabetes, and the risk of peripheral neuropathy and autonomic neuropathy is increased.[11]

Heart rate variability refers to the time variability between beats in a normal sinus rhythm in each time period, that is, heart rate fluctuations around the mean heart rate.[12]

There are changes in heart rate related to autonomic tone due to exercise, physical and emotional stress, breathing and metabolic reasons, and it is accepted as an indicator of cardiac autonomic sympathetic and parasympathetic regulation.[13]

The continuous variation of intervals between heartbeats in people with normal sinus rhythm is physiological, and the decrease in heart rate variability indicates autonomic dysfunction.[12] Therefore, measurement of heart rate variability in Holter ECG draws attention as a non-invasive method that can be used to indirectly evaluate the autonomic nervous system.[14]

The first thing to look at in the measurement of heart rate variability is the analysis of successive R waves measured on the ECG. Although it is essentially a P wave that reflects the sino-atrial output, R waves that are measured more easily are preferred.[12] Different methods can be applied to detect RR intervals. After ECG records are made, heart rate variability parameters are calculated with the help of programs, abnormal early beats are removed from the record, and measurement can be accepted if at least 85% of the recorded R waves are normal R. [15] Heart rate variability measurement is mostly made from the recordings obtained during Holter monitoring, normal-normal (NN) R intervals, which are measured by the program that processes the data in Holter, are taken as a basis for the measurement.[12]

Heart rate variability measurement is basically done by two methods: time measurements and frequency measurements.[12]

Time measurements: It is based on analysis of intervals between normal beats in 24-hour ECG recordings. The intervals (NN interval) between two consecutive beats coming out of the SA node are evaluated. (Table 2)

Autonomic neuropathy is a common complication of diabetes and, in practice, occurs in the form of persistent tachycardia, bladder atony, nocturnal diarrhoea, postural hypotension, excessive sweating, gastroparesis, and heart rate variability, which manifests itself with a decrease in time measurements.[16]

Cardiovascular autonomic neuropathy is an important complication that increases mortality, which can be found in 40% of diabetic patients. While the five-year survival rate of a patient without neuropathy is reported as 99%, this rate decreases to 60-75% in a patient with clinically significant autonomic neuropathy.[17]

It has been determined that the presence of autonomic neuropathy in diabetic patients is an unfavourable prognostic factor.[17] For the diagnosis and follow-up of cardiac autonomic neuropathy, time-dependent heart rate variability is a noninvasive method that is more sensitive than classical cardiovascular reflex tests and is easy to repeat in practice.[17]

Patients with diabetes should be questioned in terms of signs and symptoms of autonomic neuropathy. Clinically unaware of autonomic neuropathy, hypoglycemia can be seen as resting tachycardia, orthostatic hypotension, decreased heart rate variability, sudden cardiac death, silent myocardial infarction, gastroparesis, faecal incontinence, constipation, diarrhoea, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction (decreased or increased sweating).

**Table 2.** Common heart rate variability time measures [12]

| Variable | Unit | Definition |
|---|---|---|
| **Mean NN** | ms | Cycle length between two normal beats |
| **Day/night difference** | ms | The difference in the mean NN intervals obtained during the day and night |
| **SDNN** | ms | Standard deviation of all NN intervals throughout the study |
| **SDNN index** | ms | Average of standard deviations of all NN intervals over 5 min recordings |
| **SDANN** | ms | Standard deviation of the mean NN interval over the 5-min recordings |
| | | Number of adjacent NN intervals with a difference of more than 50 ms |
| **pNN50** | % | NN 50 divided by the total number of NN. |
| **rMSSD** | ms | Square root of the sum of the squares of the differences of consecutive NN |

NN: Normal-to-Normal, SDNN: Standard Deviation of NN intervals, SDNN index: Standard Deviation of NN intervals index, SDANN: Standard Deviation of the Average NN intervals, NN50: Number of NN intervals differing by more than 50 ms, pNN50: Percentage of NN50 intervals, rMSSD: Root Mean Square of Successive Differences

Frequency measurements: This method separates heart rate signals according to their frequency and intensity. (Table 3)

**Table 3.** Heart rate variability frequency measures[12]

| Parameter | | Frequency (Hz) | Specifications | Recording time |
|---|---|---|---|---|
| **HF** | High-frequency band | 0.15-0.40 | -Related to parasympathetic activation<br>-Affected by breathing | Short (1-5 min) and long |
| **LF** | Low-frequency band | 0.04-0.15 | -Reflects sympathetic and parasympathetic tone<br>-Thermoregulation and peripheral<br>Relates to vasomotor activity | Short (1-5 min) and long |
| **MF** | Mid-frequency band | 0.05-0.20 | -Reflects sympathetic and parasympathetic tone<br>-Related to baroreceptor activity | Short (1-5 min) |
| **VLF** | Very low frequency band | 0.0033-0.04 | -Unknown | Short (1-5 min) and long |
| **ULF** | Ultra-low frequency band | <0.0033 | -Unknown | Long (>24 hours) |

HF: High-Frequency band, LF: Low-Frequency band, MF: Mid-Frequency band, VLF: Very Low Frequency band, ULF: Ultra-Low Frequency band

## Materials and Methods

The study was approved by the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Ufuk University, with application date and number 20200703/16. This retrospective comparative study was conducted at the Ufuk University Dr. Rıdvan Ege Hospital, affiliated with the Faculty of Medicine at Ufuk University. Prediabetic Patients and age- and sex-matched controls who presented to the cardiology outpatient clinic between January 2018 and January 2020. and underwent Holter ECG monitoring were screened.

Patients with thyroid dysfunction, overt diabetes, arrhythmias, or those using drugs affecting heart rate or oral antidiabetic drugs were excluded. Prediabetic patients were identified based on fasting plasma glucose (FPG) values of 100–125 mg/dL and HbA1c of 5.7–6.4%, extracted from medical records. Patients with thyroid dysfunction, overt diabetes, arrhythmias, or those using drugs affecting heart rate were excluded.

All patients underwent 24-hour Holter ECG for some clinical indications, such as atypical chest pain, palpitations, or routine cardiovascular risk evaluation. Sampling was consecutive during the study period. Comparability between groups was ensured by matching for age and sex; baseline clinical variables were collected to assess potential confounding. HRV parameters—including SDNN, SDANN, rMSSD, pNN50, triangular index, and frequency-domain indices (LF, HF, VLF, LF/HF)—were calculated using validated software, after removing ectopic or artefact beats and ensuring ≥85% analyzable NN intervals.

Approximately 150 files were reviewed, and only 25 prediabetic patients were selected. Exclusion criteria were strictly followed, and patients who did not meet the criteria were not included; therefore, the sample size remained limited.

When choosing the control group patients, patients with at least two different fasting blood glucose values below 100 mg/dl were included. All participants underwent 24-hour ambulatory ECG monitoring using a 5-lead Holter device (NorthEast Monitoring Inc. DR200 Holter Recorder) to evaluate heart rate variability. Recordings were analysed with the Northeast Holter Analysis System software automatically.

ECG recordings were reviewed, and artefacts and ectopic beats were automatically identified by the software and manually checked when necessary. Only normal-to-normal (NN) intervals were included in the HRV analysis. Recordings were considered valid if at least 85% of the total R–R intervals were suitable for analysis after artefact and ectopic beat correction.

Time-domain parameters included SDNN, SDANN, rMSSD, pNN50, and triangular index. Frequency-domain parameters included very low frequency (VLF: 0.0033–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.40 Hz), and the LF/HF ratio. Frequency bands were defined according to standard international guidelines. The frequency bands are in accordance with the 1996 standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.

The primary HRV endpoint was predefined as rMSSD. This parameter was chosen because it is a reliable and reproducible indicator of short-term parasympathetic (vagal) activity and is commonly used in clinical studies evaluating autonomic function.

Secondary endpoints included time-domain parameters (SDANN, SDNN index, SDNN, and pNN50) and frequency-domain parameters (LF, HF, and LF/HF ratio).

Data distribution was assessed using normality tests. Variables with normal distribution were compared using Student's t-test, whereas non-normally distributed variables were analysed with the Mann–Whitney U test.

To minimise the risk of Type I error due to multiple comparisons, the Bonferroni correction was applied. As eight HRV parameters were evaluated, the adjusted level of statistical significance was set at $\alpha = 0.00625$.

Effect sizes were calculated to better interpret the magnitude of differences between groups. Cohen's d was used for parametric analyses, and r ($Z/\sqrt{N}$) was calculated for non-parametric analyses. Effect sizes were interpreted as small, medium, or large according to conventional thresholds (0.2, 0.5, 0.8 for Cohen's d; 0.1, 0.3, 0.5 for r).

Heart rate variability in the Holter ECG was interpreted, and it was investigated whether there was a statistical difference between the prediabetic patients and the control group.

The SPSS 22.0 package program was used for data analysis. Percentages and numbers for categorical variables, mean, standard deviation, median, minimum, and maximum values were calculated for numerical variables. The compliance of continuous numerical data with the normal distribution was evaluated visually with a histogram, statistically with Shapiro wilk, Kolmogorov-Smirnov, Skewness, and Kurtosis tests. The Student t-test was used in the comparisons between two independent groups with normal distribution, the Mann-Whitney U test was used for two independent groups without normal distribution, p value was considered statistically significant at 0.05 and below.

## Results

25 patients and 25 control groups were included in the study, which consists of 50 individuals in total. The patient and control groups were selected to be similar in terms of age and gender. (Table 4)

**Table 4.** Patient and control group characteristics

| | **Patient (n=25)** | **Control (n=25)** |
|---|---|---|
| **Age** | 56.2±9* | 54.7±14* |
| **Male** | 10 | 9 |
| **Women** | 15 | 16 |
| **HbA1c (%)** | 5.90±0,19* | - |
| **FPG** | 106±4.33* | 90.2±7.3* |
| **Creatinine** | 1.23±1.51* mg/dL | 0.81±0.14* mg/dL |
| **TSH** | 1.66±0.85* uIU/mL | 1.97±1.82* uIU/mL |
| **sT4** | 1.00±0.13* ng/dL | 0.98±5* ng/dL |

HbA1c: Hemoglobin A1c, FPG: Fasting Plasma Glucose, TSH: Thyroid Stimulating Hormone, sT4: Serum Thyroxine (Free T4), *Mean±SD

Patients with fasting blood glucose values above 100 g/dl and HbA1c values between 5.7-6.4% were included in the study. None of the patients was using oral antidiabetic drugs, patients with heart failure, arrhythmia, using drugs that affect heart rate (β-blockers, etc.), patients with overt diabetes, patients with thyroid dysfunction, or patients with chronic kidney failure were excluded from the study.

The patient group consisted of 25 people, with an average age of 56.2, including 10 men and 15 women. The mean value of HbA1c was 5.9%. The average value of fasting blood glucose was found to be 106 mg/dl. In the patient group, the mean creatinine value was 1.23 mg/dL, the TSH value was 1.66 uIU/mL, and free T4 was 1 uIU/mL.

In the control group, the mean age was 54.7 years; 9 of the individuals in this group were men, and 16 were women. The mean fasting blood glucose value was 90.2 mg/dl. In the control group, the mean creatinine value was 0.81, the TSH value was 1.97 uIU/mL, and free T4 was 0.98 uIU/mL.

For Table 5, normality of each parameter was assessed using the Shapiro–Wilk test. Variables with normal distribution were analysed using Student's t-test (mean ± SD reported), non-normal variables using Mann–

Whitney U test (median [IQR] reported). For Table 6, normality of each variable was assessed using the Shapiro–Wilk test. Both the Triangle Index and VLF were normally distributed, Student's t-test was used, and the results are presented as mean ± SD. When we consider the heart rate variability parameters, it was seen that all parameters, the average of which was calculated, were lower in the patient group than in the control group. Among these values, the time parameters SDANN, rMSSD, pNN50 and Triangle index were statistically significant. Frequency parameters HF, VLF, and LF/HF were statistically significant. (Tables 5 and 6)

**Table 5.** Control and patient group heart rate variability parameters*

| Parameter | Groups | N | Median | Mean±SD | Z | P value | Effect Size (95% CI) |
|---|---|---|---|---|---|---|---|
| **SDANN** | Control | 25 | 116 | 140.56±60.95 | -1.99 | 0.05 | r=0.28(0.00–0.52) |
| | Patient | 25 | 119 | 113±23.53 | | | |
| **SDNNİ** | Control | 25 | 130 | 59.74±23.71 | -1.7 | 0.09 | r=0.24 (-0.04–0.49) |
| | Patient | 25 | 126 | 57.52±34.38 | | | |
| **SDNN[1]** | Control | 25 | 55 | 142.7±39.57 | t:2.03 | 0.048 | d=0.60 (0.03-1.16) |
| | Patient | 25 | 51 | 123.11±20.5 | | | |
| **rMSSD** | Control | 25 | 31 | 34.67±19.43 | -2.3 | 0.02 | r=0.32 |
| | Patient | 25 | 23 | 26.81±11.97 | | | (0.04–0.55) |
| **LF** | Control | 25 | 415 | 551.26±377.7 | -0.86 | 0.38 | r=0.12 |
| | Patient | 25 | 460 | 469.54±344.5 | | | (-0.16–0.39) |
| **HF** | Control | 25 | 178 | 304.9±314.82 | -2.26 | 0.02 | r=0.32 |
| | Patient | 25 | 108 | 168.98±6.36 | | | (0.04–0.55) |
| **LF/HF** | Control | 25 | 2,54 | 2.94±1.97 | -0.58 | 0.50 | r=0.08 |
| | Patient | 25 | 3,46 | 3.61±1.93 | | | (-0.20–0.35) |
| **pNN50** | Control | 25 | 7 | 11.07±10.49 | -2.09 | 0.04 | r=0.29 |
| | Patient | 25 | 4 | 6.78±7.42 | | | (0.01–0.53) |

SDANN: Standard Deviation of the Average NN intervals, SDNNi: Standard Deviation of NN intervals index, SDNN: Standard Deviation of NN intervals, rMSSD: Root Mean Square of Successive Differences, LF: Low-Frequency band, HF: High-Frequency band, LF/HF: Low Frequency to High Frequency ratio, pNN50: Percentage of NN50 intervals [1]:Student's t-test, * Mann whitney U test

**Table 6.** Control and patient group heart rate variability parameters*

| Parameter | Patient (n=25) | Control (n=25) | Statistic | P Value |
|---|---|---|---|---|
| Triangle I. | 22.1±5.46 | 27.3±9.94 | t:2.65 | 0.01 |
| VLF (ms $^2$) | 859.33±285.77 | 1115.29±415 | t:2.47 | 0.02 |

*Student's t-test, Triangle I.: Triangular Index, VLF: Very Low Frequency band

*Primary Endpoint*

rMSSD was lower in the patient group compared with the control group (26.81±11.97 vs 34.67±19.43; p=0.02). The effect size was moderate (r=0.32; 95% CI: 0.04–0.55). However, after Bonferroni correction for multiple comparisons (adjusted α=0.00625), this difference was no longer statistically significant.

*Secondary Endpoints*

SDNN values were lower in the patient group (p=0.048), with a moderate effect size (Cohen's d=0.60; 95% CI: 0.03–1.16).

HF was also reduced in patients (p=0.02), showing a moderate effect size (r=0.32; 95% CI: 0.04–0.55).

Similarly, pNN50 was lower in the patient group (p=0.04), with a small-to-moderate effect size (r=0.29; 95% CI: 0.01–0.53).

No statistically significant differences were observed for SDANN, SDNN index, LF, or LF/HF ratio. These parameters demonstrated small effect sizes (r<0.30).

After Bonferroni adjustment, none of the secondary endpoints remained statistically significant. Therefore, these results should be interpreted as exploratory.

## Discussion

Autonomic neuropathy in diabetes is a complication that should be considered because of the cardiovascular effects it may cause. Previous studies suggest that autonomic neuropathy may develop in the early stages of diabetes, and some evidence indicates that similar alterations may also be present during the prediabetic stage. Our findings are consistent with the possibility that early alterations in cardiac autonomic regulation may already be present during the prediabetic stage. In our study, we found that autonomic neuropathy can start in prediabetic patients with high blood glucose and HbA1c but who do not fully meet the diagnostic criteria for diabetes.

Many previous studies have shown that cardiac autonomic neuropathy is common in diabetes and is generally associated with reduced heart rate variability.[18]

According to a study conducted by H Kudat et al.[19] in 2006, heart rate variability parameters were found to be lower in diabetic patients compared to the control group. Similarly, in our study, all heart rate variability time and frequency parameters were found to be lower in the prediabetic group, which we defined as the patient group, compared to the control group.

In the study conducted by H Kudat et al. with 31 diabetic patients and 30 control groups, it was found that heart rate variability decreased in diabetic patients compared to the control group in a statistically significant manner in SDNN, SDANN, SD, pNN50, rMSSD, LF, HF, and Total Power parameters, except for Mean NN and LF/HF parameters.

In this study, which we conducted with 25 prediabetic patients and 25 control groups, the mean of heart rate variability parameters was found to be lower in the prediabetic group than in the control group in all parameters calculated. In our study, time parameters SDANN, rMSSD, pNN50 and Triangle index were statistically significant. Frequency parameters HF, VLF, and LF/HF were statistically significant. On the other hand, SDNN, SDNNi and LF parameters were not statistically significant, but the prediabetic group was lower than the control group. Due to certain limitations, the fact that the prediabetic patient sample was not numerically high was thought to affect statistical significance in all parameters.

In the study of Charlotte Coopmans et al.[20] published in Diabetes Care in 2020, the data of 550 prediabetic and 331 diabetic patients were examined, and heart rate variability time and frequency parameters were found to be lower than those of the population with normal glucose metabolism, and this decrease was found to be correlated with HbA1c and fasting blood glucose values in patient groups.

According to Fred Shaffer and JP Ginsberg, the SDNN parameter is one of the most important parameters evaluating cardiac risk and is one of the parameters that shows a decrease in cardiac autonomic neuropathy.[21] The decrease in this parameter may be directly related to cardiac mortality. In our study, a mean decrease of approximately 20 ms in the mean SDNN values was found in the prediabetic group compared to the control group. Although there was no significant decrease, this decrease in heart rate variability in cardiac autonomic neuropathy caused by prediabetes is a warning for cardiovascular complications.

Again, according to Fred Shaffer and JP Ginsberg, it was stated that low rMSSD values may be associated with sudden cardiac death, and in our study, rMSSD values were found to be significantly lower in the prediabetic group compared to the control group. (prediabetic group: 26.81±11.97 control group: 34.67±19.43).[21] This again shows that cardiac autonomic neuropathy, which may develop in prediabetes, is a complication that should be considered, and its early diagnosis is important.

In our study, the mean value of fasting blood sugar was found to be 106 mg/dl. In the patient group, the mean creatinine value was 1.23 uIU/mL, the TSH value was 1.66 uIU/mL, and free T4 was 1 uIU/mL.

The mean fasting blood glucose value was found to be 90.2 mg/dl. In the control group, the mean creatinine value was 0.81 mg/dL, the TSH value was 1.97 uIU/mL, and free T4 was 0.98 uIU/mL. There was no significant difference between the patient and control groups in terms of creatinine, TSH and T4 values. As expected, there was a significant difference between the means of fasting blood glucose values.

Heart rate variability measurement draws attention as a very popular, easily applicable noninvasive method that we can use to determine autonomic regulation of the heart and has direct prognostic value for cardiovascular risk.[22]

Diabetes directly affects the cardiovascular system with its macro and microvascular complications and causes serious cardiovascular problems such as myocardial infarction, stroke, intermittent claudication, sudden death, arrhythmias, silent ischemia and heart failure.[20] Diabetes is also directly related to atherothrombosis and endothelial dysfunction.[20] In addition to all these effects, cardiac autonomic neuropathy is a condition that we are perhaps not very aware of the damage caused by diabetes in the cardiovascular system, which starts quietly but early, but needs to be cared for, recognised early and treated with the results it creates.

This study provides preliminary evidence that HRV parameters may be lower in prediabetic individuals compared to normoglycemic controls. All heart rate variability parameters were lower than those of the control group and can be considered as an indicator of cardiac autonomic neuropathy. No significant decrease was detected in some time and frequency parameters, which can be considered a limitation of our study, which was

caused by the small number of patients. These findings suggest that HRV may be reduced in prediabetes, consistent with possible early autonomic involvement.

Although several HRV parameters demonstrated moderate effect sizes suggestive of reduced vagal modulation in the patient group, statistical significance was attenuated after correction for multiple testing. These findings may indicate clinically relevant autonomic alterations; however, given the limited sample size and multiplicity adjustment, they should be interpreted as hypothesis-generating and require confirmation in adequately powered prospective studies.

It is possible to obtain more precise results in studies with similar large numbers of patients and multicenter studies. It is important and necessary to conduct new studies in the form of case-control with a larger number of patients on the subject to prove the onset of cardiac cotonoma neuropathy in prediabetes.

*Study Limitations*

Heart rate variability is influenced by several metabolic and clinical factors, including hypertension, dyslipidemia, obesity, smoking status, and underlying cardiovascular comorbidities. Due to the retrospective design of the present study and limitations in available medical records, detailed data regarding these potential confounding variables were not consistently accessible. Therefore, adjustment for these factors could not be performed.

**Ethical Considerations:** The study was approved by the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Ufuk University, with application date and number 20200703/16.

**Conflict of Interest:** The authors declare no conflict of interest.

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# EMERGENCY DEPARTMENT CONSULTATIONS IN THE GREEN ZONE: FREQUENCY, SPECIALTIES, AND OUTCOMES

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## Abstract

**Objectives:** The green zone covers patients with stable vital signs who do not require urgent intervention; however, due to the high number of presentations, this group constitutes a significant portion of the emergency department workload. This study aimed to determine the characteristics of consultations requested for green zone patients in the emergency department and to reveal their impact on emergency department operations.

**Materials and Methods:** Our study was conducted retrospectively on adult patients who visited the emergency department green zone between June 2024 and May 2025. The demographic characteristics of patients who required consultation, the speciality for which consultation is requested, the time of consultation, the diagnosis code, and patient outcomes were analysed.

**Results:** In our study, 75,011 green zone applications were reviewed, and it was determined that consultations were requested for 237 patients (0.32%). The most frequently requested speciality was orthopaedics (47.3%), followed by plastic surgery (8.0%), ear, nose, and throat (6.3%), and paediatrics (5.9%). 70% of patients for whom consultations were requested were admitted, and 29.5% were discharged. The rate of admission to the intensive care unit was significantly higher in patients who were consulted by cardiology ($p<0.001$).

**Conclusion:** Although the consultation rate among green zone patients is low, the majority of these patients have serious clinical conditions requiring hospitalisation. Proper management of the consultation process is important for both patient safety and the efficient use of emergency department resources. Strengthening primary care services may play an important role in the management of low-acuity patients in emergency departments.

**Keywords:** Emergency medical services, primary health care, referral and consultation, triage.

## Introduction

Emergency departments are units with the highest patient admissions and operate 24 hours a day. In Türkiye, the number of emergency department visits ranges between 100 and 130 million annually, accounting for 31.6% of total hospital visits in 2016 and 48.6% in 2021.[1] Due to increasing patient admissions over the years, the functions of emergency departments in both diagnosis and treatment have become more complex.

Triage systems aim to reduce this complexity by classifying patients according to their level of urgency. These systems enable the efficient use of healthcare resources, reduce waiting times in emergency departments, and help lower morbidity and mortality rates.[2] In Türkiye, patient triage in emergency departments is carried out according to three color codes, as specified in the "Communication on the Procedures and Principles for the Implementation of Emergency Department Services in Inpatient Health Facilities" published by the Ministry of Health: red zone (life-threatening), yellow zone (stable but requiring urgent intervention), and green zone (vital signs stable, not requiring urgent intervention).[3, 4]

Green zone patients generally represent stable individuals without life-threatening conditions. However, they constitute a substantial proportion of emergency department visits in Türkiye and may contribute significantly to emergency department crowding. [5,6] Many of these patients could potentially be managed at the primary care level.[7]

A large proportion of complaints from green zone patients consist of symptoms related to minor trauma, musculoskeletal complaints, and upper respiratory tract infection symptoms.[8] However, in some patients, unexpected findings may emerge after the initial assessment, and consultation with specialists may be required. Appropriate consultations requested in emergency departments increase diagnosis and treatment optimisation, while inappropriate consultation requests can prolong waiting times and reduce emergency department efficiency. Appropriate consultation requests are critical in terms of patient satisfaction and emergency department performance.[9]

It has been determined that the rate of consultations requested from emergency departments worldwide varies between 20% and 40%.[10,11] Studies conducted in Türkiye show that this rate generally ranges between 6% and 20%.[12,13] Studies on green zone patients in the literature are quite limited. Determining the consultation needs of green zone patients, who constitute a large proportion of emergency department visits, can provide valuable information for emergency department management from both clinical and administrative perspectives.

In our study, the characteristics, timing, and outcomes of consultations requested for green zone patients in the emergency department of a tertiary education and research hospital were examined; the data obtained were evaluated by comparing them with the literature. Our study aimed to determine the characteristics of consultations requested from the emergency department green zone and to reveal their impact on emergency department operations.

## Materials and Methods

*Study design*

Our study was designed as a single-centre retrospective observational study. The study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee of Bilecik Şeyh Edebali University (Date: 30/10/2025, Decision No: 10/8).

Patients who visited the emergency department green zone of a tertiary education and research hospital between June 2024 and May 2025 were examined, and patients requiring consultation were included in the study.

In our institution, triage is performed by trained emergency nurses in accordance with the nationally implemented three-level colour-coded triage system used widely in emergency departments across Türkiye. Patients are categorised as red, yellow, or green based on clinical severity, vital signs, and presenting complaint. Patients whose vital signs are stable, who do not have a life-threatening emergency, and whose complaints are assessed as low priority have been triaged as green zone patients.

As an inclusion criterion, all patients directed to the green zone during their initial visit were evaluated in our study, and all patients who requested at least one specialist consultation during their stay in the emergency department were analysed. No patients who requested consultation from the green zone were excluded from the study.

Patients were excluded if they were triaged to the red or yellow zones at initial presentation. In addition, green zone patients for whom no specialist consultation was requested during their emergency department stay were not included in the analysis. Patients with incomplete or missing electronic medical records were also excluded to ensure data accuracy and reliability. Furthermore, individuals who left the emergency department before being evaluated or before completion of their clinical assessment were excluded from the study.

*Data collection*

Data obtained from the hospital information management system was used. Patients' demographic information (age, gender), requested consultation departments, consultation times (during/after hours), diagnosis codes (ICD-10), outcomes (discharge, admission, referral), and admission units were recorded.

*Statistical Analysis*

Data analysis was performed using IBM SPSS 25.0 software. Descriptive statistics are presented as counts and percentages for categorical variables. The normality of numerical variables was assessed using the Shapiro-Wilk test. Variables that fitted a normal distribution are expressed as mean ± standard deviation (SD), while variables that did not fit a normal distribution are expressed as median and min-max. The Chi-square test and Fisher's Exact test were used in the analysis of categorical variables; the Mann-Whitney U test was used in the analysis of numerical variables that did not conform to a normal distribution in independent groups. The statistical significance level was accepted as $p<0.05$.

Because the study aimed to describe the characteristics, timing, patterns, and outcomes of consultations requested for green zone patients, no predictive modelling was planned. Therefore, multivariable analyses such as logistic regression were not performed. The study does not aim to establish causal relationships or determine independent predictors of hospitalisation; rather, it aims to present a descriptive profile of consultation practices in green zone patients.

## Results

It was determined that 75,011 patients visited the emergency department's green zone between June 2024 and May 2025. Of these patients, 237 (0.32%) were referred to specialist departments. The demographic data of the patients, consultation times, outcomes, and distribution of hospitalised patients according to the units they were admitted to are presented in Table 1.

**Table 1.** The demographic data of the patients, consultation times, outcomes and distribution of hospitalised patients according to the units they were admitted to

| | | |
|---|---|---|
| **Age** | | Median (min-max) |
| | Year | 41 (0-91) |
| **Sex** | | n (%) |
| | Female | 96 (40.5%) |
| | Male | 141 (59.5%) |
| **Consultation Time** | | n (%) |
| | Working Hours | 101 (42.6%) |
| | Outside Working Hours | 136 (57.4%) |
| **Outcome** | | n (%) |
| | Discharged | 70 (29.5%) |
| | Admitted to the Hospital | 166 (70.0%) |
| | Transferred | 1 (0.5%) |
| **Hospital Admission Unit** | | n (%) |
| | Ward | 160 (96.4%) |
| | Intensive Care Unit | 6 (3.6%) |

When examining the age distribution of the patients consulted, the median age was found to be 41 (0-91). The median age for male patients was 38 (0-89), while the median age for female patients was 54 (3-91). It was determined that the age values for male patients were statistically significantly lower than those for female patients. (p=0.005, Mann-Whitney U test)

When consultation numbers were evaluated, it was determined that consultations were requested for an average of 0.65 patients per day.

The distribution of the 15 most common diagnosis codes among patients requiring consultation is shown in Figure 1. The distribution of departments requested for consultation is shown in Figure 2. The distribution of departments requesting consultations and the times at which consultations were requested is provided in Table 2.

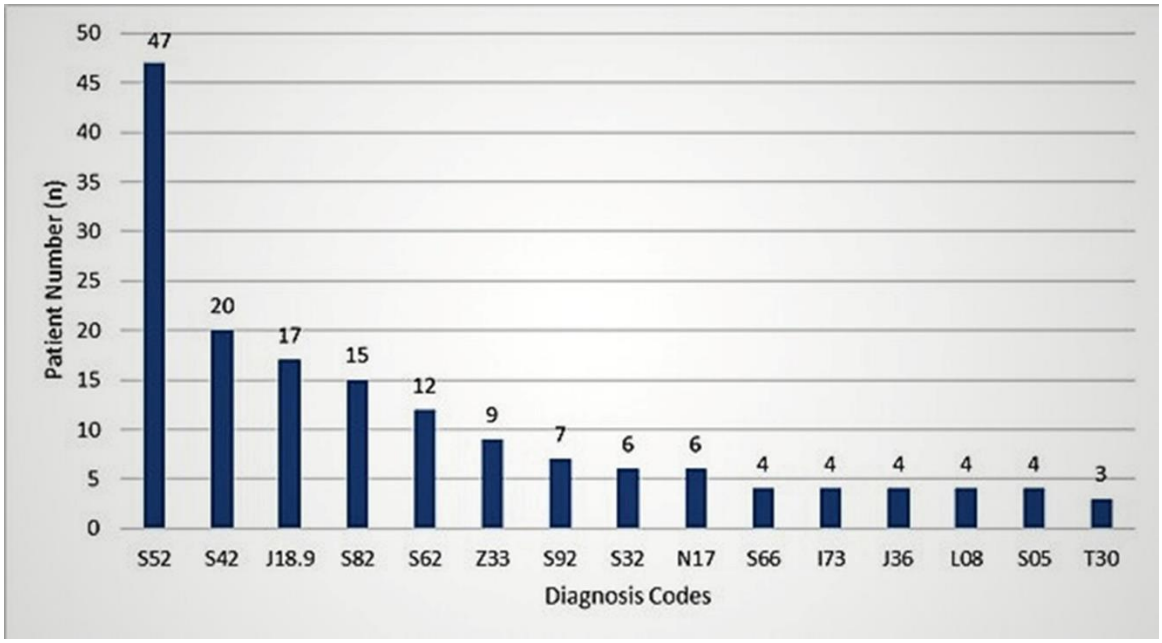


**Figure 1.** The distribution of the 15 most common diagnosis codes among patients requiring consultation

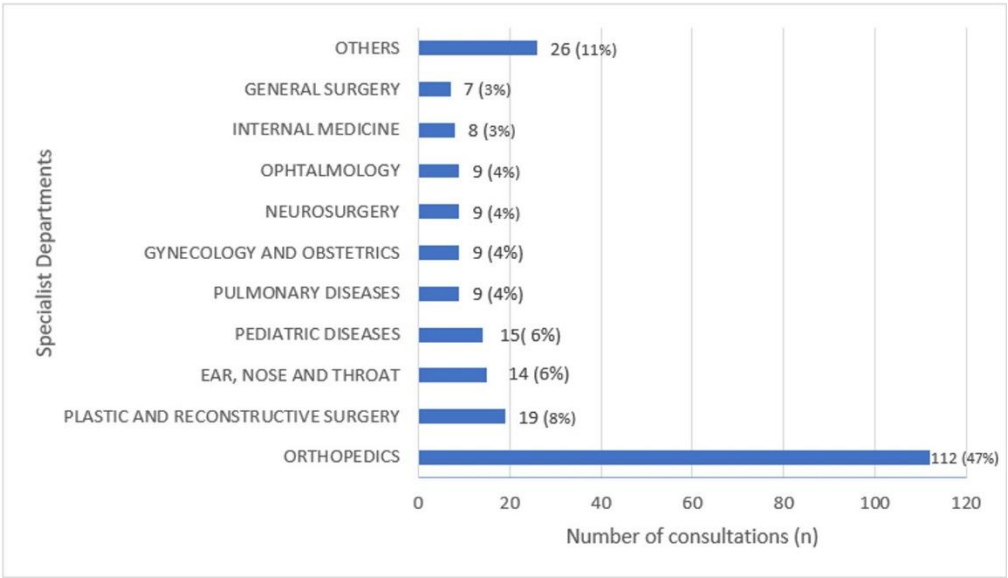


**Figure 2.** The distribution of departments requested for consultation

**Table 2.** The distribution of departments requesting consultations and the times at which consultations were requested

| Departments Requesting Consultations | Working Hours n (%) | Outside Working Hours n (%) |
|---|---|---|
| **Ear, Nose, and Throat** | 2 (13.3%) | 13 (86.7%) |
| **Pediatric Diseases** | 5 (35.7%) | 9 (64.3%) |
| **Orthopedics** | 51 (45.5%) | 61 (54.5%) |
| **Neurology** | 0 (0.0%) | 3 (100.0%) |
| **Gynaecology and Obstetrics** | 4 (44.4%) | 5 (55.6%) |
| **Plastic and Reconstructive Surgery** | 12 (63.2%) | 7 (36.8%) |
| **General Surgery** | 3 (42.9%) | 4 (57.1%) |
| **Cardiology** | 1 (20.0%) | 4 (80.0%) |
| **Neurosurgery** | 5 (55.6%) | 4 (44.4%) |
| **Pediatric Surgery** | 2 (66.7%) | 1 (33.3%) |
| **Internal Medicine** | 4 (50.0%) | 4 (50.0%) |
| **Cardiovascular Surgery** | 4 (39.5%) | 0 (39.5%) |
| **Gastroenterology** | 2 (39.5%) | 0 (39.5%) |
| **Infectious Diseases** | 2 (40.0%) | 3 (60.0%) |
| **Ophthalmology** | 3 (33.3%) | 6 (66.7%) |
| **Pulmonary Diseases** | 1 (11.1%) | 8 (88.9%) |
| **Psychiatry** | 0 (0.0%) | 1 (100.0%) |
| **Urology** | 0 (0.0%) | 2 (100.0%) |
| **Thoracic Surgery** | 0 (0.0%) | 1 (100.0%) |

Patient ages were evaluated according to the departments requested for consultation, and it was determined that the departments with the highest median ages were neurology at 77 (75-85) years, internal medicine at 74 (29-91) years, and urology at 73 (64-82) years. The departments with the lowest median ages were pediatrics with 7 (0-15) years, pediatric surgery with 14 (3-17) years, and otorhinolaryngology with 22 (4-46) years. A box plot graph showing the age distribution of patients according to consultation departments is provided in Figure 3.

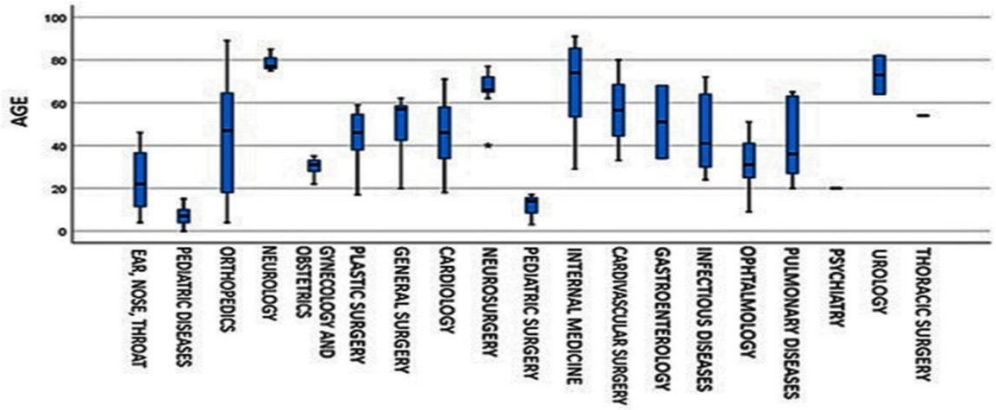


**Figure 3.** Box plot graph of the age distribution of patients according to the consultation speciality departments

When examining the departments requesting consultations and the gender ratio, it was determined that among consultations requested from the orthopaedics department, there were 52 female patients (46.4%) and 60 male patients (53.6%). In consultations requested from the plastic and reconstructive surgery department, the number of female patients was 4 (21.1%) and the number of male patients was 15 (78.9%); in consultations requested from the ear, nose, and throat department, the number of female patients was 5 (33.3%) and the number of male patients was 10 (66.7%).

The age distribution was evaluated according to patient outcomes, and the median age of discharged patients was found to be 38 (4-82), while the median age of hospitalised patients was 45 (0-91), with no statistically significant difference found between the groups. (p=0.208, Mann-Whitney U test) When evaluating the relationship between the units where patients were admitted and their age groups, the median age of patients admitted to the ward was 45 (3-91), while the median age of patients admitted to the intensive care unit was 46 (0-87), and no statistically significant difference was found between the groups. (p=0.866, Mann-Whitney U test)

When evaluated by gender groups according to patient outcomes, it was determined that 26 (37.1%) of the discharged patients were female and 44 (62.9%) were male. Among patients admitted to the hospital, 70 (42.2%) were female, and 96 (57.8%) patients were male. One patient transferred to an external centre was male. No statistically significant difference was found between the groups (p=0.549, Chi-square Test). When the gender groups of hospitalized patients were evaluated according to the units they were admitted to, it was determined that 68 (42.5%) of the patients admitted to the ward were female and 92 (57.5%) were male. 2 (33.3%) of the patients admitted to the intensive care unit were female and 4 (66.7%) were male. No statistically significant difference was found between the groups. (p=1.000, Fisher's Exact Test)

The relationship between the speciality departments requested for consultation and patient outcomes was examined, and as outcomes of orthopaedic consultations, 15 (13.4%) patients were discharged, and 97 (86.6%) patients were admitted. As a result of plastic and reconstructive surgery consultations, 11 (57.9%) patients were discharged, and 8 (42.1%) patients were admitted; as a result of ear, nose, and throat consultations, 8 (53.3%) patients were discharged, and 7 (46.7%) patients were admitted. All 9 (100.0%) patients referred to neurosurgery were discharged, while all 8 (100.0%) patients referred to internal medicine and all 9 (100.0%) patients referred to pulmonary medicine were admitted. When evaluating the relationship between the departments requested for consultation and the units where admission was given, 4 (100.0%) patients referred to the cardiology department were admitted to the intensive care unit, and no patients were admitted to the ward. Of the patients referred to the pediatric department, 1 (10.0%) was admitted to the intensive care unit, and 9 (90.0%) were admitted to the ward; of the patients referred to the orthopaedics department, 1 (1.0%) was admitted to the intensive care unit, and 96 (99.0%) were admitted to the ward. Patients admitted to all other departments were admitted to the ward. A statistically significant difference was found between the groups, and the significant difference was found between the cardiology department and the other departments. ($p<0.001$, Chi-Square Test)

## Discussion

Our study demonstrated that the overall consultation rate among green zone patients was 0.32%, which is considerably lower than the overall consultation rates reported for all triage areas in emergency departments in Türkiye.[12,13] However, most studies evaluate consultation patterns across all emergency department triage categories, whereas our analysis focused specifically on green zone patients. Since these patients typically present with low-acuity conditions and can often be managed directly by emergency physicians, consultation requests are expected to occur less frequently. This finding is consistent with previous studies reporting that a substantial proportion of low-acuity emergency department presentations can be effectively evaluated and treated without specialist involvement.[14, 15] Therefore, the lower consultation rate in our study likely reflects the characteristics of the green zone population rather than differences in consultation practices.

The fact that orthopaedics is the most frequently consulted speciality in the green zone, with a ratio of 47.3%, is consistent with many studies in the literature. In the study by Şener et al., the ratio of orthopaedic consultations to all consultations was determined to be 12.2%, while in the study by Gülaçtı et al., this ratio was found to be 30.8%.[13,16] Considering that the most common diagnosis codes identified in patients requiring consultation were for forearm, upper arm, and shoulder fractures, it can be inferred that orthopaedic consultation is frequently requested due to upper extremity injuries. Furthermore, the fact that plastic surgery and otorhinolaryngology are also frequently consulted fields can be explained by the prevalence of facial and extremity injuries in this group of patients.

The time periods during which consultations were requested were examined, and it was determined that 57.4% of consultations were requested outside of working hours. When reviewing the literature on the rates of consultations requested outside of working hours, Leblebici et al. found that 66% of consultations were requested outside of working hours, while Leithead et al. found that 57.8% of consultations were requested outside of working hours.[17, 18] The results of our study are consistent with the literature. Due to the absence of outpatient services during non-working hours, patients can only use emergency departments to receive healthcare services. Increasing green zone density, especially in hospitals in large cities, makes the efficient use of emergency department resources difficult. Since all patients are evaluated in emergency departments, consultation rates may also increase in this context.

In our study, it was determined that consultations were requested for 0.32% of green zone patients, but the admission rate among these patients was 70%. In this context, it was found that the admission rate among green zone applications was 0.22%. When green zone hospital admission rates were examined in the literature, Alnasser et al. reported a rate of 0.4%, Honigman et al. reported a rate of 4.0%, and Leey-Echavarría et al. reported a rate of 6.4%.[19-21] According to the results of our study, the admission rates of green zone patients are low when evaluated in comparison with the international literature. The high number of emergency department visits in our country and the triage system's classification of a large group of patients as green zone may be the reasons for this difference. In addition, the fact that emergency departments partially take over primary health care services leads to many outpatient clinic visits being directed to the emergency department. In other countries, the definition of green zone is narrower and only covers patients with mild symptoms who are suitable for outpatient treatment. Therefore, although the proportion of cases requiring consultation among green zone patients is low, it is clinically important that the majority of these cases require hospitalisation for further evaluation and treatment. Our findings indicate that the consultation process in emergency departments needs to be carefully planned, and unnecessary referrals should be prevented.

In Türkiye, emergency departments are often used as a primary access point to healthcare, particularly for patients with low-acuity conditions. Studies based on the perspectives of family medicine describe how it would be possible to manage a large portion of the emergency department patient population at the primary care level.[7,22] Strengthening the integration between emergency departments and primary care services may improve patient flow and reduce unnecessary emergency department utilisation.

Despite the low consultation frequency, the hospitalisation rate among consulted green zone patients was notably high. This suggests that green zone patients who require specialist consultation represent a clinically distinct and potentially more severe subgroup. Similar findings have been reported in tertiary care settings, where patients for whom consultation is requested demonstrate higher admission rates and greater clinical severity.[23,24] The high admission rate may reflect selective and appropriate consultation practices by

emergency physicians, cautious triage decisions in borderline cases, and, in a limited number of instances, possible under-triage at initial presentation. Emergency department triage decisions are made rapidly based on initial clinical presentation and vital signs. Consequently, some patients may initially appear clinically stable but later demonstrate disease progression or previously unrecognised severity. Therefore, a small proportion of patients initially classified as green zone may subsequently require more advanced care.

Our study found that patients requiring cardiology consultation had a statistically significantly higher rate of intensive care unit admission. This suggests that some green zone patients may have been assessed in a low triage category due to inadequate risk assessment at the time of presentation. A review of the literature shows that errors in triage threaten patient safety, and therefore triage systems need to be strengthened with objective, transparent, and evidence-based criteria. The most important factors affecting patient safety in the triage process include accurate and continuous patient assessment, experienced personnel, and the use of objective criteria.[25,26] High workload, lack of experience, and subjective assessments can negatively affect patient safety. When the results of our study are evaluated in conjunction with the literature, it is evident that the triage system, which is critical for patient safety, needs to be strengthened with objective criteria.

An important operational finding of our study was that the majority of consultations were requested outside regular working hours. This pattern suggests a disproportionate increase in emergency department workload during off-hours, when outpatient services are unavailable and access to specialist care is limited. In this context, proper management of the consultation process and strengthening the role of family medicine in the management of low-acuity patients are essential for maintaining patient safety and ensuring the efficient use of emergency department resources.

This study has several limitations. First, due to its single-centre retrospective design, the generalizability of the findings may be limited. Second, the statistical analysis was primarily descriptive, as the main aim of the study was to present the characteristics and outcomes of consultations requested for green zone patients rather than to develop predictive models. Although this approach was appropriate for the exploratory nature of the study, future multicenter prospective studies with larger datasets may allow more advanced statistical modelling to identify predictors of consultation requests and hospitalisation.

**Ethical Considerations:** The study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee of Bilecik Şeyh Edebali University (Date: 30/10/2025, Decision No: 10/8).

**Conflict of Interest:** The authors declare no conflict of interest.

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# VALIDATION OF WITNESS-DERIVED SECONDARY CINCINNATI PREHOSPITAL STROKE SCALE SCORES FOR PREHOSPITAL STROKE TRIAGE

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**Abstract**

**Objectives:** Prehospital delay in acute ischemic stroke is driven by decision delay between symptom recognition and taking action. Although witnesses recognise symptoms early, the value of translating witness-reported symptoms into standardised stroke assessment tools remains unclear. This study aimed to evaluate the predictive value of witness-derived, physician-administered secondary Cincinnati Prehospital Stroke Scale (CPSS) scores.

**Materials and Methods:** This prospective, cross-sectional validation study was conducted in a tertiary ED between August and November 2025. Secondary CPSS scores were independently assigned by two blinded emergency physicians using the three-item CPSS, based on structured interviews with untrained witnesses of stroke-like patients. Predictive validity was assessed using final ED diagnoses, and decision delay was derived from standardised prehospital timelines. Statistical analyses included Cohen's kappa, diagnostic accuracy metrics, and chi-square tests.

**Results:** A total of 235 patient–witness pairs were included. More than 70% of witnesses delayed action for over 30 minutes, accounting for 56.3% of prehospital delay. Interrater reliability was substantial ($\kappa$ = 0.788). Secondary CPSS scores showed low sensitivity and negative predictive value but high specificity and positive predictive value, indicating limited rule-in utility. Scores ≥1 were not associated with shorter decision delay (p = 0.789).

**Conclusion:** Secondary CPSS based on witness reports is reliably scored but has limited diagnostic accuracy and does not facilitate faster decision-making, limiting its utility as a standalone tool for prehospital stroke triage. Future studies should address cognitive barriers and improve witness response.

**Keywords:** Stroke, bystanders, risk assessment, decision making, predictive value of tests, emergency department.

## Introduction

In patients with stroke-like symptoms, prehospital delay (PD) comprises decision delay (DD)—from symptom recognition to seeking help—and transfer delay (TD), from help activation to hospital arrival. DD is the main contributor to total delay (PD).[1-2] Despite advances in acute stroke care, reperfusion therapy reaches only 1%–8% of eligible patients, underscoring the need for improved public stroke recognition.[3] Prehospital timelines are influenced by behavioural, logistical, emergency medical service (EMS)-related, and socioeconomic factors.[2-10] Witness presence, public settings, not living alone, and accurate symptom recognition shorten DD.[2-6] In contrast, denial, misattribution, limited knowledge, reduced mobility, chronic illness, and delayed or absent EMS activation prolong DD, reflecting patient- and witness-level decision-making and routing choices during the prehospital period.[5-12] Primary care services are frequently contacted early in the symptom trajectory. Therefore, understanding how patients and witnesses navigate "first-contact" options and how these decision processes influence EMS activation and time to hospital arrival is critical for optimising stroke awareness strategies and strengthening time-sensitive prehospital triage.[4, 6, 7, 12]

Stroke witnesses are often the first to observe neurological symptoms and can substantially influence DD.[4] Although the Cincinnati Prehospital Stroke Scale (CPSS) is a validated screening tool when used by healthcare professionals,[13-20,] its validation based on witness-guided scoring remains limited. To our knowledge, this study is the first to evaluate the diagnostic accuracy of witness-derived Cincinnati Prehospital Stroke Scale (CPSS) scores. These scores were obtained through structured interviews conducted by blinded emergency physicians with untrained witnesses in the emergency department (ED). It also examines their association with decision delay and whether performance varies by witness characteristics. This study examines whether witness descriptions within the CPSS framework can be translated into standardised, measurable clinical indicators. The findings aim to inform the development of witness-focused prehospital stroke triage awareness strategies. These strategies target early recognition, first-contact choices, and subsequent routing decisions while integrating with primary care pathways.

### *Cincinnati Prehospital Stroke Scale*

The CPSS is a brief screening tool based on three clinical signs: facial droop, arm drift, and speech abnormality.[13] It was originally developed for paramedics, physicians, and other EMS providers to rapidly identify suspected stroke. CPSS-related studies can be grouped into four categories: reproducibility studies by prehospital providers;[13-18] ED-based reproducibility and comparative studies by emergency physicians;[19, 20] dispatcher-guided telephone assessments;[21, 22] and lay bystander studies evaluating recognition of CPSS-equivalent signs rather than formal scoring.[23, 24] Each abnormal finding scores 1 point

(range 0–3), and a score ≥1 indicates high stroke probability. The CPSS demonstrated 66% sensitivity and 87% specificity in the original study[13] and sensitivities of 75%–95% with specificities of 24%–100% in external validations.[14-20]

The primary objective was to evaluate the predictive value of witness-derived secondary CPSS scores in the ED. The secondary objective was to assess associations between secondary CPSS scores, decision delay, and witness characteristics. Hypothesis 1: Witness-derived secondary CPSS scores predict ischemic stroke. Hypothesis 2: Secondary CPSS scores ≥1 are associated with shorter decision delay.

## Materials and Methods

This prospective, analytical, cross-sectional validation study was conducted in the ED of Ankara Bilkent City Hospital, a tertiary academic hospital in Ankara, Türkiye and approved by the Medical Research, Scientific and Ethical Evaluation Board of Ankara Bilkent City Hospital (Project No: TABED 1-25-1588; August 13, 2025). The study followed the STROBE guidelines (Supplementary File 1). Clinical Trials ID: NCT07277790; Dec 14, 2025. Written informed consent was obtained from all participants, and data were anonymised and handled in accordance with the Declaration of Helsinki.

### *Study setting and flow*

The study was conducted in a tertiary academic ED in Ankara Bilkent City Hospital, Türkiye, between August 15 and November 15, 2025. Witness interviews were performed face-to-face by two blinded emergency physicians (a senior resident and an attending physician) during initial patient assessment.

The study comprised two phases (Figure 1). Phase 1 assessed interrater reliability, in which a senior emergency medicine resident and an attending emergency physician independently assigned secondary CPSS scores after standardised orientation and CPSS training. Emergency team assistant staff received a brief 20-minute protocol training focused on data collection and blinding procedures. The two raters completed a 30-minute CPSS training. Phase 2 evaluated predictive validity by comparing secondary CPSS scores with final diagnoses and assessing associations with witness characteristics and decision delay.

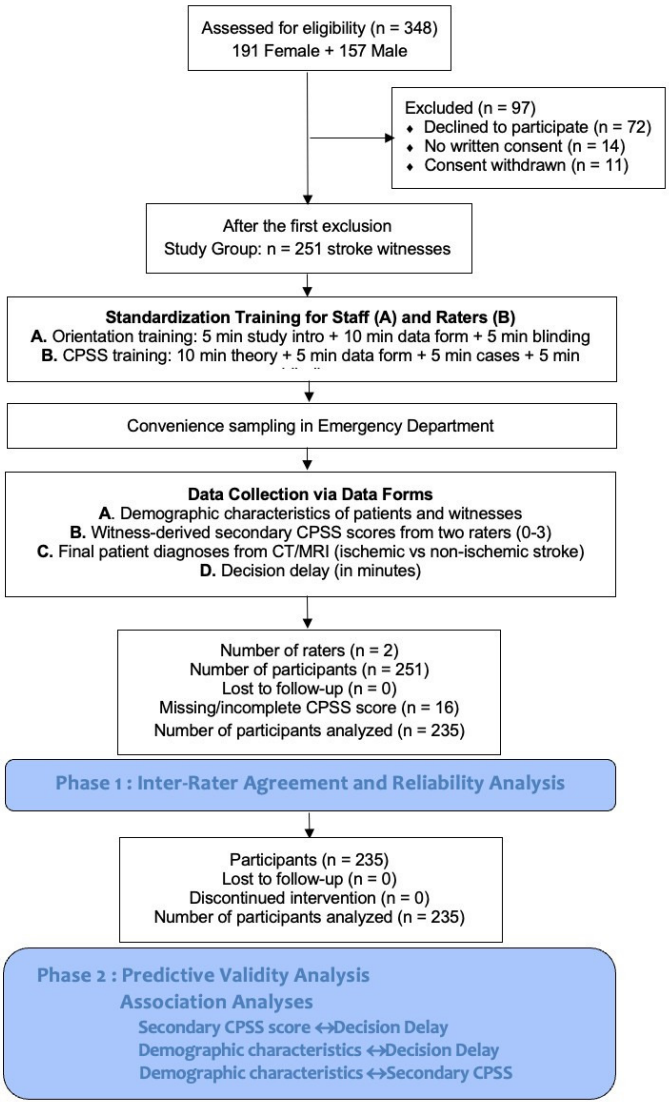


**Figure 1.** Study design and participant flow diagram

*Study population and sample size*

Suspected stroke patients were defined as individuals presenting sudden facial asymmetry, arm weakness, speech disturbance, or other focal neurological deficits, who underwent neuroimaging to confirm or exclude stroke.[22] Suspected stroke refers to cases in which clinicians in the emergency department consider stroke as a possible diagnosis based on the clinical presentation. In contrast, stroke-like symptoms denote a broader, symptom-based construct that may also arise from various neurological or metabolic conditions and therefore do not imply a definitive diagnosis. In this study, stroke-like symptoms were defined as signs observed by witnesses or relatives. Patients presenting with such symptoms were included based on clinical

suspicion of stroke in the emergency department. Neuroimaging was performed in most patients as part of routine evaluation, but was not defined as a mandatory inclusion criterion.

Eligible participants were adult witnesses (≥18 years) who directly observed the onset of stroke-like symptoms. Witnesses were required to accompany the patient during ED evaluation and to be the primary decision-makers for EMS activation or private transport. Convenience sampling was used. Witnesses were primarily family members but also included friends, neighbours, or caregivers. Witness exclusion criteria were defined based on both witness-related criteria and predefined patient-related conditions. Witnesses were excluded if they had cognitive impairment, prior stroke-recognition training, a healthcare professional background, were not the decision-maker for EMS activation or transport, refused to provide informed consent, or had incomplete CPSS-based interview data. In addition, witnesses were excluded if the accompanying patient had been transferred with a confirmed stroke diagnosis.

Sample size was calculated using G*Power based on a 7.4% prevalence of stroke-like presentations in the ED,[22] an assumed odds ratio of 1.8, $\alpha = 0.05$, and 80% power. The required sample size was 182; accounting for attrition, the target was 228. Of 348 eligible witnesses, 235 met the inclusion criteria and provided informed consent.

*Outcomes and variables*

Primary CPSS was assigned directly by healthcare providers through patient examination, whereas secondary CPSS was derived by blinded emergency physicians based solely on witness reports. The primary outcomes were witness-derived secondary CPSS scores and final patient diagnoses. Secondary outcomes included decision delay and witness characteristics. The main independent variable was the secondary CPSS score (range 0–3), derived from structured ED interviews with witnesses. Decision delay (DD) was the study's dependent variable, defined as the time between symptom recognition and taking action. As quantitative variables, secondary CPSS scores (0–3) were analysed as continuous and dichotomised variables (≥1 vs. 0), and decision delay was analysed continuously and categorically (<30 vs. ≥30 minutes). Witness characteristics were treated as potential confounders, while perceived symptom clarity or severity and contextual factors were considered potential effect modifiers.

*Data collection instruments*

Data were collected prospectively using two structured research data forms. Secondary CPSS scores were derived from standardised witness interviews (Supplementary Files 2). Each CPSS item was scored dichotomously (yes/no). Unmarked or "I don't know" responses were considered incomplete. Total CPSS scores ranged from 0 to 3, and two blinded raters independently scored each report. Emergency team

assistant staff documented final diagnoses, demographics, and prehospital timeline variables (Supplementary Files 3). Predictive validity was assessed by comparing secondary CPSS scores with final diagnoses. For final diagnoses, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) findings were interpreted by radiologists blinded to the study. Data were entered into a secure database, anonymised, and analysed by an independent statistician. Secondary CPSS scores were not used to guide clinical decision-making and had no impact on the timing of patient diagnosis or treatment.

*Blinding and bias*

Physicians were blinded to clinical findings, final diagnoses, and each other's assessments, while witnesses were blinded to patient examination findings and final diagnoses. Selection bias was minimised through consecutive sampling. Standardised interviews, protocolized training, blinding, and timeline clarification reduced information, interviewer, recall, observer, and diagnostic review bias. Social desirability bias was addressed by assuring participants that responses would not influence patient care.

*Statistical analysis*

Analyses were performed using IBM SPSS Statistics for Mac (Version 31.0). Interrater reliability was assessed using Cohen's kappa with 95% confidence intervals. Diagnostic accuracy metrics were calculated from 2×2 contingency tables using CT or MRI as the reference standard. Two-tailed p-values $<0.05$ were considered statistically significant.

**Results**

Figure 1 summarises the flow of eligible participants. The study population comprised 235 patients and their 235 accompanying stroke witnesses. Among witnesses, the mean age was 44.1 years; most were aged 18–65 years (90.2%) and were predominantly first-degree relatives (83.0%). More than half were female (53.2%) and employed (57.0%), and educational attainment varied, with 31.9% having a tertiary education. Decision delay was substantial: 72.4% initiated action more than 30 minutes after symptom recognition, and 60.9% waited more than 60 minutes. (Table 1). Median prehospital delay was 240 minutes, largely driven by a median decision delay of 135 minutes, whereas median transport time was shorter at 45 minutes. All time intervals showed wide variability (Table 1).

**Table 1.** Witness demographic characteristics

| **Witness demographics** | | | |
|---|---|---|---|
| **Variables** | Characteristics | Measurement | |
| | | n | % |
| **Age (years)** | 18-65 | 212 | 90.2 |
| | >65 | 23 | 9.8 |
| **Gender** | Female | 125 | 53.2 |
| | Male | 110 | 46.8 |
| **Degree of relationship** | First-degree relative | 195 | 83.0 |
| | Not a first-degree relative | 40 | 17.0 |
| **Education level** | Illiterate | 12 | 5.1 |
| | Primary | 65 | 27.7 |
| | Secondary | 83 | 35.3 |
| | Tertiary | 75 | 31.9 |
| **Employment status** | Employed | 134 | 57.0 |
| | Unemployed | 101 | 43.0 |
| **Decision delay (min)** | <10 | 20 | 8.5 |
| | 10-30 | 45 | 19.1 |
| | 31-60 | 27 | 11.5 |
| | >60 | 143 | 60.9 |
| **PD = DD + TD** | Mean (SD) | Median (IQR) | Min-Max Values |
| **Prehospital delay (PD) (min)** | 1005.5 (2176.0) | 240.0 (90.0 - 945.0) | 15.0 - 18600.0 |
| **Decision delay (DD) (min)** | 885.3 (2153.2) | 135.0 (30.0 - 780.0) | 1.0 - 18570.0 |
| **Transport delay (TD) (min)** | 120.2 (319.1) | 45.0 (30.0 - 85.0) | 5.0 - 2700.0 |

First-degree relative: Spouse, child, mother, father, sibling. Not first-degree relative: Other family members, friends and neighbours. Primary: Literate and elementary school. Secondary: Middle and /high school. Tertiary: University. Unemployed: Housewife, or retired. SD: Standard deviation. IQR: Interquartile Range (25%-75%).

Among the 235 patients, the mean age was 63.2 years; 56.6% were older than 65 years, and 51.9% were female. Most lived with family members (86.4%) and arrived by private vehicle (57.4%). CT or MRI imaging was performed in more than 90% of cases. Final diagnoses showed that 73.2% had ischemic stroke and 9.4% had hemorrhagic stroke. A total of 22 hemorrhagic stroke cases were identified. However, one patient had both subarachnoid and intraparenchymal haemorrhage; therefore, the descriptive statistics of haemorrhage subtypes include 23 events. Hypertension was the most common risk factor (34.0%). The most frequent presenting symptoms were slurred speech (35.3%) and arm weakness (30.6%) (Table 2).

**Table 2.** Patient demographic characteristics

| Patient Demographics | | | |
|---|---|---|---|
| **Variables** | **Characteristics** | **n** | **%** |
| **Age (years)** | 18-65 | 102 | 43.4 |
| | >65 | 133 | 56.6 |
| **Gender** | Female | 122 | 51.9 |
| | Male | 113 | 48.1 |
| **Living style** | Alone | 12 | 5.1 |
| | With family members | 203 | 86.4 |
| | Living with assistance | 20 | 8.5 |
| **Education level** | Illiterate | 49 | 20.9 |
| | Primary | 110 | 46.8 |
| | Secondary | 38 | 16.2 |
| | Tertiary | 38 | 16.2 |
| **Employment status** | Employed | 161 | 68.5 |
| | Unemployed | 74 | 31.5 |
| **Transfer way to the hospital** | Ambulance | 94 | 40.0 |
| | Private vehicle | 135 | 57.4 |
| | Outpatient | 6 | 2.6 |
| **CT scan** | Done | 224 | 95.3 |
| | Not done | 11 | 4.7 |
| **MRI scan** | Done | 220 | 93.6 |
| | Not done | 15 | 6.4 |
| **Exitus** | Yes | - | - |
| | No | 235 | 100.0 |
| **Diagnoses** | Ischemia | 172 | 73.2 |
| | Hemorrhage | 22 | 9.4 |
| | Other CNS diagnoses | 27 | 11.5 |
| | Non-CNS diagnoses | 34 | 14.5 |
| **Ischemic stroke** | Cerebral | 110 | 64.0 |
| | Cerebellar | 20 | 11.6 |
| | Transient ischemic attack | 42 | 24.4 |
| **Hemorrhage** | Subarachnoid | 7 | 30.4 |
| | Subdural | 4 | 17.4 |
| | Epidural | - | - |
| | Intraparenchymal | 11 | 47.8 |
| | Cerebellar | 1 | 4.4 |
| **Risk factors** | Hypertension (HT) | 80 | 34.0 |
| | Diabetes mellitus (DM) | 29 | 12.3 |
| | Hyperlipidemia (HPL) | 10 | 4.3 |
| | Coronary artery disease | 28 | 11.9 |
| | Atrial fibrillation | 6 | 2.6 |
| | HT + DM | 21 | 8.9 |
| | HT + DM + HPL | 8 | 3.4 |
| | Others | 211 | 89.7 |
| **Symptoms** | Facial droop | 25 | 10.6 |
| | Arm drift | 72 | 30.6 |
| | Slurred speech | 83 | 35.3 |
| | Face + arm + speech | 3 | 1.3 |
| | Others | 151 | 64.2 |

Living with assistance: Nursing home/Home care. Primary: Literate and elementary school. Secondary: Middle and /high school. Tertiary: University. Unemployed: Jobless, housewife, or retired. CT: Computed Tomography. MRI: Magnetic Resonance Imaging. CNS: Central Nervous System

Interrater agreement for secondary CPSS scoring was high. As shown in Table 3, both raters assigned a CPSS score of 0 in 38.3% of cases, while scores of 1, 2, and 3 were assigned in 48.5%, 11.9%, and 1.3%, respectively. Per cent agreement for individual CPSS items was high (93.6%–95.7%), with kappa coefficients indicating substantial to almost perfect agreement (facial droop: $\kappa = 0.791$; arm drift: $\kappa = 0.848$; slurred speech: $\kappa = 0.889$; all $p < 0.001$). Overall agreement for total CPSS scores was 84.7%, with $\kappa = 0.788$ (95% CI: 0.726–0.850; $p < 0.001$) (Table 4).

**Table 3.** Cross-tabulation of total Cincinnati Prehospital Stroke Scale (CPSS) scores by emergency medicine (EM) resident and emergency medicine attending physician

| **Raters** | **EM Attending Physician n (%)** | | | | |
|---|---|---|---|---|---|
| **EM Resident n (%)** | **CPSS** | **0** | **1** | **2** | **3** | **Total** |
| | **0** | 86 (36.6) | 4 (1.7) | - | - | 90 (38.3) |
| | **1** | - | 98 (41.7) | 16 (6.8) | - | 114 (48.5) |
| | **2** | - | 16 (6.8) | 12 (5.1) | - | 28 (11.9) |
| | **3** | - | - | - | 3 (1.3) | 3 (1.3) |
| | **Total** | 86 (36.6) | 118 (50.2) | 28 (11.9) | 3 (1.3) | 235 (100.0) |

EM: Emergency medicine, CPSS: Cincinnati Prehospital Stroke Scale

**Table 4.** Inter-rater agreement on Cincinnati Prehospital Stroke Scale (CPSS) items: EM resident vs. EM attending physician

| **CPSS Items** | **Percent agreement (%)** | **Kappa (κ) [95% CI]** | **p-value** |
|---|---|---|---|
| **Facial droop** | 95.7 | 0.791 (0.666 to 0.916) | <0.001 |
| **Arm drift** | 93.6 | 0.848 (0.774 to 0.922) | <0.001 |
| **Slurred speech** | 94.9 | 0.889 (0.828 to 0.950) | <0.001 |
| **Total** | 84.7 | 0.788 (0.726 to 0.850) | <0.001 |

CPSS: Cincinnati Prehospital Stroke Scale

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In predictive validity analyses, secondary CPSS components demonstrated low-to-moderate sensitivity (12.2%–43.0%) with consistently high specificity (74.6%–98.4%). Among individual components, slurred speech showed the most favourable diagnostic profile, with a sensitivity of 43.0%, specificity of 85.7%, PPV of 89.2%, and the highest accuracy (54.5%). Arm drift demonstrated moderate sensitivity (32.6%) and strong specificity (74.6%), with an accuracy of 43.8%, whereas facial droop showed low sensitivity (12.2%) but high specificity (93.7%). PPVs were generally high (>82%), with comparatively lower values for arm drift (77.8%) and the full triad (66.7%); while NPVs remained uniformly low (26%–35%). Combined CPSS item pairs and the full triad yielded very high specificity (>93%) but very low sensitivity (1.2%–11.1%), resulting in modest accuracy values (27%–33%). Positive likelihood ratios were low to moderate across individual CPSS components (PLR range: 1.28–3.01) and low for combined patterns (PLR ≤2.56), indicating limited rule-in capability. Negative likelihood ratios were uniformly high (NLR range: 0.66–1.00), reflecting poor rule-out performance. Accuracy values were low, ranging from 27.2% to 54.5% across individual items and combinations (Hypothesis 1) (Table 5).

**Table 5.** Reliability and predicting performance metrics of the CPSS and its components with frequencies (%) and (95% confidence intervals)

| Items | Sensitivity | Specificity | PPV | NPV | PLR | NLR | Accuracy |
|---|---|---|---|---|---|---|---|
| **Facial droop** | 12.21 (7.72 to 18.06) | 93.65 (84.53 to 98.24) | 84.0 (65.22 to 93.63) | 28.10 (26.41 to 29.85) | 1.92 (0.69 to 5.38) | 0.94 (0.86 to 1.02) | 34.04 (28.01 to 40.49) |
| **Arm drift** | 32.56 (25.62 to 40.11) | 74.60 (62.06 to 84.73) | 77.78 (68.53 to 84.91) | 28.83 (25.33 to 32.61) | 1.28 (0.80 to 2.06) | 0.90 (0.76 to 1.08) | 43.83 (37.39 to 50.43) |
| **Slurred speech** | 43.02 (35.51 to 50.78) | 85.71 (74.61 to 93.25) | 89.16 (81.43 to 93.91) | 35.53 (31.86 to 39.37) | 3.01 (1.61 to 5.65) | 0.66 (0.56 to 0.78) | 54.47 (47.87 to 60.96) |
| **Face + arm** | 2.91 (0.95 to 6.65) | 98.41 (91.47 to 99.96) | 83.33 (37.33 to 97.67) | 27.07 (26.28 to 27.88) | 1.83 (0.22 to 15.37) | 0.99 (0.95 to 1.03) | 28.51 (22.83 to 34.74) |
| **Face + speech** | 4.07 (1.65 to 8.21) | 98.41 (91.47 to 99.96) | 87.50 (46.77 to 98.24) | 27.31 (26.45 to 28.19) | 2.56 (0.32 to 20.43) | 0.97 (0.93 to 1.02) | 29.36 (23.62 to 35.63) |
| **Arm + speech** | 11.05 (6.78 to 16.71) | 93.65 (84.53 to 98.24) | 82.61 (62.70 to 93.07) | 27.83 (26.19 to 29.53) | 1.74 (0.62 to 4.92) | 0.95 (0.87 to 1.03) | 33.19 (27.20 to 39.61) |
| **Face + arm + speech** | 1.16 (0.14 to 4.14) | 98.41 (91.47 to 99.96) | 66.67 (15.58 to 95.59) | 26.72 (26.04 to 27.42) | 0.73 (0.07 to 7.94) | 1.00 (0.97 to 1.04) | 27.23 (21.65 to 33.40) |

CPSS: Cincinnati Prehospital Stroke Scale, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive Likelihood Ratio NLR: Negative Likelihood Ratio.

Witnesses with CPSS ≥1 did not act faster than those with CPSS = 0; the proportion acting within 30 minutes was similar (63.1% vs. 36.9%; p = 0.789). Accordingly, higher secondary CPSS scores were not associated with shorter time to action (Hypothesis 2) (Table 6). No demographic factors—including age, gender, relationship to the patient, education, or employment status—were significantly associated with secondary CPSS scores (all p > 0.05). Likewise, none were significantly associated with decision delay (≤30 min vs. >30 min), with p-values ranging from 0.113 to 0.504 (Table 6)

**Table 6.** The association of secondary CPSS scores and witness demographic characteristics with decision delay

| **Variables** | **Secondary CPSS score n (%)** | | | **Decision delay n (%)** | | |
|---|---|---|---|---|---|---|
| | **CHIS=0** | **CHIS≥1** | **p*** | **≤30 Min.** | **>30 Min.** | **p*** |
| **Age (years)** | | | | | | |
| 18-65 | 82 (91.1) | 130 (89.7) | 0.715 | 60 (92.3) | 152 (89.4) | 0.504 |
| >65 | 8 (8.9) | 15 (10.3) | | 5 (7.7) | 18 (10.6) | |
| **Gender** | | | | | | |
| Female | 45 (50.0) | 80 (55.2) | 0.440 | 40 (61.5) | 85 (50.0) | 0.113 |
| Male | 45(50.0) | 65 (44.8) | | 25 (38.5) | 85 (50.0) | |
| **Degree of relationship** | | | | | | |
| First-degree relative | 76 (84.4) | 119 (82.1) | 0.638 | 51 (78.5) | 144 (84.7) | 0.255 |
| Not a first-degree relative | 14 (15.6) | 26 (17.9) | | 14 (21.5) | 26 (15.3) | |
| **Education level** | | | | | | |
| İlliterate | 4 (4.4) | 8 (5.5) | 0.647 | 5 (7.7) | 7 (4.1) | 0.390 |
| Primary | 21 (23.3) | 44 (30.3) | | 19 (29.2) | 46 (27.1) | |
| Secondary | 34 (37.8) | 49 (33.8) | | 25 (38.5) | 58 (34.1) | |
| Tertiary | 31 (34.4) | 44 (30.3) | | 16 (24.6) | 59 (34.7) | |
| **Employment status** | | | | | | |
| Employed | 57 (63.3) | 77 (53.1) | 0.124 | 33 (50.8) | 101 (59.4) | 0.232 |
| Unemployed | 33 (36.7) | 68 (46.9) | | 32 (49.2) | 69 (40.6) | |
| **Secondary CPSS score** | | | | | | |
| CPSS = 0 | - | - | - | 24 (36.9) | 66 (38.8) | 0.789 |
| CPSS ≥ 1 | - | - | - | 41 (63.1) | 104 (61.2) | |

*Pearson Chi-Square Test

## Discussion

Patient characteristics in this study—including mean age, sex distribution, hypertension prevalence, and stroke subtype distribution—were broadly comparable to those reported in prior CPSS diagnostic accuracy studies.[13,16-18] The high rate of neuroimaging use (≥94%) aligns with established CPSS validation standards.[13,15] Presenting symptoms were dominated by slurred speech and arm weakness. These features have been linked to a higher likelihood of stroke recognition and EMS activation in certain populations.[5,10] Witness demographics largely mirrored existing literature, with stroke symptoms most often observed by middle-aged family members.[4, 5, 12]

Secondary CPSS scoring demonstrated high interrater reliability. Agreement across components was substantial to almost perfect and comparable to clinician-applied CPSS studies[13-20] and dispatcher-assisted assessments.[22,23] Agreement was higher for slurred speech and arm weakness than for facial droop, consistent with prior witness-based studies.[24, 25] These results suggest that physician-assigned secondary CPSS scores derived from structured witness interviews are reproducible and methodologically robust.

Regarding predictive validity (Hypothesis 1), slurred speech showed the most favourable diagnostic profile among individual CPSS components, combining moderate sensitivity with high specificity. Other components demonstrated lower sensitivity, and combined CPSS patterns—while highly specific—showed poor sensitivity and limited accuracy. PPVs remained relatively high, particularly for slurred speech and arm drift, whereas NPVs were uniformly low, indicating limited rule-out capability. Overall, witness-derived CPSS findings provided modest rule-in value but insufficient discriminatory performance to exclude stroke, offering partial support for Hypothesis 1.

The limited sensitivity and modest accuracy observed for combined CPSS patterns, especially the full triad, likely reflect contextual features of the study population, including very high stroke prevalence and the indirect nature of witness-based assessment. In such settings, restrictive combinations preferentially identify only the most overt cases, underscoring the adjunctive rather than exclusionary role of secondary CPSS scoring in early stroke evaluation. Accordingly, secondary CPSS may be best positioned as a supplementary, rule-in–oriented tool rather than a standalone screening instrument.

Hypothesis 2, which proposed an association between higher secondary CPSS scores and shorter decision delay, was not supported. Witnesses with CPSS ≥1 did not initiate action faster than those with CPSS = 0, and no demographic characteristic was associated with CPSS scoring or timeliness. Although this contrasts with studies suggesting that symptom severity accelerates help-seeking,[2,5,10,12,26,27] recognition of stroke symptoms did not translate into timely action.[28, 29] It aligns with evidence emphasising the multifactorial

nature of prehospital delay.[7-9] Qualitative research highlights family deliberation, emotional responses, and uncertainty as key barriers to prompt EMS activation, even when symptoms are recognised.[4,12]

Decision delay accounted for more than half of the total prehospital delay, consistent with prior evidence identifying the recognition-to-decision interval as a major contributor to treatment delay.[4,5] These findings reinforce the concept of a persistent recognition–action gap in acute stroke care.

In decision-making processes shaped by uncertainty, indecision, and fear, many patients and witnesses (≈48–80%) contact primary care/family physicians first to "clarify urgency" and "validate" the situation.[4, 6, 26] While this highlights the pivotal role of primary care in early help-seeking, choosing primary care–oriented routes (telephone advice, appointments, face-to-face assessment, outpatient referral) instead of EMS activation or direct ED presentation may delay or preclude EMS involvement and is associated with longer prehospital times.[4 6,7,12,26] Despite relatively high awareness, many patients still arrive by private vehicle, reflecting persistent gaps between knowledge, recognition, response, and transport behaviours that manifest as delayed decision-making and non-EMS transport.[6-8,11,28] This reliance on non-EMS transport remains clinically relevant, as EMS use as the first contact or not calling EMS is consistently associated with shorter PD and improved access to time-sensitive reperfusion therapies.[9,10] Multiple cognitive and contextual determinants contribute to these patterns, including perceiving EMS as less accessible or appropriate and intending to call EMS but not translating that intention into action.[6, 28] Strengthening the "time is brain" message to trigger rapid emergency care-seeking remains a key priority.

The literature emphasises the need for targeted educational strategies to bridge the recognition–action gap. These strategies should promote rapid symptom recognition and triage, reinforce low-threshold EMS activation for suspected stroke, and prioritise high-risk individuals and their close contacts over broad public campaigns with uncertain cost-effectiveness.[3,30] Accordingly, awareness initiatives and targeted education for high-risk groups should be aligned with—and supportive of—primary care. In this context, witness-derived CPSS may serve as a practical, rule-in–oriented supplemental prehospital stroke triage tool to support witnesses' decision-making, whose effectiveness could be enhanced through structured primary care–based public education and technology-assisted triage strategies addressing individual differences, cognitive barriers, and contextual conditions.

*Strengths and Limitations*

This study benefits from a comparatively large sample, standardised data collection procedures, and high interrater agreement, which enhance the methodological consistency and applicability of the findings to comparable emergency care settings. A potential strength of this study is the evaluation of a witness-derived CPSS approach for stroke triage during the prehospital phase. However, several limitations should be

acknowledged. The study was conducted in a single tertiary emergency department, which may restrict external validity. Secondary CPSS scores and prehospital time intervals were derived from witness reports and are therefore subject to recall bias and subjective interpretation. The cross-sectional design precludes causal inference. Additionally, unmeasured confounders—such as health literacy, emotional response, or prior exposure to stroke—may have influenced symptom recognition and decision-making processes. Finally, exclusion of patients without accompanying witnesses may have introduced selection bias. Future multicenter investigations are warranted to further explore cognitive and contextual determinants of delayed action and to assess the effectiveness of structured CPSS-based educational or digital interventions.

**Ethical Considerations:** Ethical approval was obtained from the Medical Research, Scientific and Ethical Evaluation Board of Ankara Bilkent City Hospital (Project No: TABED 1-25-1588; approved on August 13, 2025).

**Conflict of Interest:** The authors declare no conflict of interest.

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# ACUTE HICCUPS FOLLOWING ARIPIPRAZOLE TREATMENT IN A PATIENT WITH AUTISM SPECTRUM DISORDER AND CATATONIA: A DETAILED CASE REPORT AND MANAGEMENT CHALLENGES

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## Abstract

Aripiprazole is a widely used second-generation antipsychotic known for its favourable side effect profile. Although generally well-tolerated, rare adverse reactions, such as hiccups, have been documented. We present the case of a 28-year-old male with autism spectrum disorder and psychosis with catatonic features who developed acute, persistent hiccups shortly after starting aripiprazole treatment. The patient, hospitalised for catatonia and psychotic symptoms, was initially treated with benzodiazepines and later with aripiprazole. Within 24 hours of the dose increase to 10 mg/day, he developed continuous hiccups that significantly interfered with oral intake. Aripiprazole was identified as the most likely cause; thus, the medication was discontinued, and chlorpromazine 25 mg twice daily was administered for symptomatic relief. The hiccups completely resolved within 48 hours. This case highlights that hiccups may occur across a range of aripiprazole doses and typically subside after discontinuation. Young male patients with developmental disorders and those concurrently receiving benzodiazepines may be at greater risk. Chlorpromazine may serve as an effective symptomatic option for managing aripiprazole-induced hiccups when benzodiazepine dose reduction is not feasible.

**Keywords:** Aripiprazole, autism spectrum disorder, catatonia, hiccup.

## Introduction

Aripiprazole is a second-generation antipsychotic with partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors and antagonism at 5-HT2A receptors. Its tolerability profile is generally favourable compared with other antipsychotics, with lower rates of metabolic adverse effects, extrapyramidal symptoms, and hyperprolactinemia.[1]

Hiccups, defined as involuntary, spasmodic contractions of the diaphragm and intercostal muscles, are usually benign and self-limiting; however, they can become persistent or intractable when centrally mediated. Several pharmacological agents, including corticosteroids, benzodiazepines, and antipsychotics, have been implicated as potential causes.[2] Aripiprazole-induced hiccups case series have been reported in the literature, but the patients' characteristics and treatment methods vary.[3]

Here, we present a detailed case of a young male patient with autism spectrum disorder and psychosis who developed acute hiccups after aripiprazole treatment. We discuss diagnostic considerations, potential mechanisms, and management strategies.

## Case Report

A 28-year-old single male, high-school graduate, unemployed, living with his mother, was followed for autism spectrum disorder and atypical psychosis. He was admitted to our psychiatric inpatient unit after abruptly discontinuing clozapine 500 mg/day within one week because of frequent falls resulting in multiple lower extremity fractures. On admission, he presented with catatonic symptoms, which were mutism, generalised muscular rigidity, refusal of oral intake, and posturing.

The initial work-up, including complete blood count, renal and thyroid function tests, electrolytes, electroencephalography (EEG), and cranial computerised tomography (CT), revealed no abnormalities. Brain magnetic resonance imaging (MRI) could not be performed due to orthopaedic implants from previous surgeries. The Bush-Francis Catatonia Rating Scale (BFCRS) score was 19, and the Clinical Global Impression (CGI) severity score was 7. Because lorazepam was unavailable in the market, diazepam 20 mg/day was initiated and titrated up to 40 mg/day. His catatonic symptoms were partially remitted.

By day 7, he developed psychotic symptoms, including talking to himself, staring at a fixed point, and stating he was "searching for himself on Google." Olanzapine 10 mg/day was added, and diazepam dosage decreased to 30 mg/day as catatonia improved. By day 15, however, he developed sedation, psychomotor slowing, mutism, posturing, and urinary incontinence. BFCRS score rose to 21, and olanzapine was discontinued.

Electroconvulsive therapy (ECT) was considered but deferred by the orthopedist because of active, unstable lower extremity fractures. Diazepam was replaced with lorazepam, titrated up to 12 mg/day.

Approximately 15 days later, catatonic symptoms resolved, but psychotic symptoms reemerged, including visual hallucinations and mystical delusions as "communicating with angels and paradise". Given the history of recurrent falls under clozapine treatment, lack of response to risperidone and paliperidone, and limited response to olanzapine, aripiprazole 5 mg/day was started and increased to 10 mg/day after three days.

Soon after increasing aripiprazole treatment to 10 mg/day, he developed acute, day-long hiccups that impaired oral intake. Cardiac, pulmonary, and neurological evaluations were unremarkable, and repeat cranial CT remained normal. In addition, gastrointestinal etiologies (reflux-related symptoms and abdominal discomfort), metabolic abnormalities (electrolyte imbalance, renal/hepatic dysfunction), infectious signs (fever, inflammatory markers), and other non-drug-related triggers were systematically considered and not supported by clinical assessment or laboratory results. Based on the temporal association and exclusion of other possible causes, aripiprazole-induced hiccups were suspected, and the drug was discontinued on the second day of symptoms. Chlorpromazine 25 mg was administered twice daily for symptomatic relief, and the hiccups resolved completely within 48 hours.

He remained clinically stable and continued on lorazepam 4 mg/day for three weeks. The plan was to reduce the benzodiazepine dose gradually. During his follow-up, olanzapine was administered again due to ongoing psychotic symptoms. No recurrence of hiccups was observed. His final CGI severity score was 5, and global improvement was rated as 2. The patient was discharged with olanzapine 5 mg/day and lorazepam 3 mg/day, and continues to be followed as an outpatient.

## Discussion

Aripiprazole-related hiccups, though rare, are clinically important because they may interfere with nutrition, hydration, and medication adherence. In a systematic review of 29 cases, it was reported that hiccups most frequently appeared within 1–2 days of starting or increasing aripiprazole and resolved within 1–4 days after discontinuation, regardless of dose (2.5–30 mg/day).[3] Our patient's presentation, onset shortly after starting aripiprazole treatment, and complete remission within 48 hours of discontinuation, align with these findings.

Young age, male sex, and neurodevelopmental disorder may increase susceptibility.[3] Additionally, benzodiazepine co-administration has been associated with a marked increase in hiccup risk. Benzodiazepines enhance GABA(A) receptor activity, which may facilitate activation of the medullary "hiccup reflex arc." A retrospective study reported a 70-fold increased risk in patients receiving both aripiprazole and

benzodiazepines, particularly in men.[4,5] In our case, the benzodiazepine dose could not be reduced due to ongoing catatonic symptoms, which may have augmented the risk of hiccups.

The most effective management strategy is the reduction or discontinuation of aripiprazole, leading to resolution in most cases within a few days.[6,7] Adjunctive pharmacological measures, such as chlorpromazine, gabapentin, or baclofen, can be used when symptoms are severe or persistent.[5,8,9] In our patient, discontinuation of aripiprazole combined with chlorpromazine administration resulted in rapid improvement.

Persistent hiccups (>48 h) in primary care should prompt a brief structured assessment, including symptom severity, impact on oral intake, and a focused medication review, with particular attention to recently initiated or dose-escalated antipsychotics and concomitant benzodiazepines. Red flags such as focal neurological findings, cardiopulmonary symptoms, fever, persistent vomiting, weight loss, or inability to maintain oral intake should warrant urgent referral. Supportive measures and empiric treatment for possible gastroesophageal reflux with a proton pump inhibitor or an H2-receptor antagonist may be considered when clinically appropriate, and chlorpromazine can be used for severe symptoms, along with discontinuation of the suspected causative medication.

This case emphasises that hiccups should be considered as a potential adverse effect, particularly in male patients on benzodiazepines, during aripiprazole titration. Prompt recognition and discontinuation of aripiprazole can prevent complications such as dehydration and aspiration risk and improve treatment adherence. Additionally, chlorpromazine may be considered as an effective symptomatic option for managing acute hiccups in these patients.

**Ethical Considerations:** Written informed consent was obtained from the patient, and all personal information has been kept confidential.

**Conflict of Interest:** The authors declare no conflict of interest.

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# HETEROZYGOUS FAMILIAL HYPOBETALIPOPROTEINEMIA DETECTED DURING PERIODIC EXAMINATION IN A FAMILY MEDICINE OUTPATIENT CLINIC: A CASE REPORT

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## Abstract

Familial hypobetalipoproteinemia (FHBL) is a rare, genetically inherited cause of hypocholesterolemia. Although it usually presents asymptomatically, it can occasionally lead to clinical outcomes such as hepatic steatosis. In this case, a 37-year-old male patient presented to a family medicine outpatient clinic for a routine health check. His physical examination and vital signs were within normal limits. Laboratory investigations revealed markedly low LDL and total cholesterol levels and elevated triglycerides. Additionally, mild elevations in liver enzymes and grade 1–2 hepatic steatosis on abdominal ultrasonography were detected. A presumptive diagnosis of heterozygous familial hypobetalipoproteinemia was considered, and the patient was referred to the endocrinology clinic for further evaluation. This case demonstrates how periodic health screening in asymptomatic individuals can contribute to the early detection of rare metabolic disorders. Family physicians are competent in evaluating patients holistically and initiating appropriate referrals based on clinical and laboratory findings.

**Keywords:** Familial hypobetalipoproteinemia, hypocholesterolemia, hepatic steatosis, periodic health examination, family medicine, lipid disorders.

## Introduction

Family medicine serves as the cornerstone of primary healthcare and plays a central role in the provision of preventive services. As emphasised by the Ministry of Health and the Turkish Association of Family Physicians, periodic health examinations enable the early detection of diseases before the appearance of symptoms. Within this scope, periodic health examinations are effective in screening for systemic conditions such as cardiometabolic diseases, dyslipidemia, hypertension, and obesity.[1] According to the literature, family physicians are expected to effectively assess patient needs, formulate initial diagnostic impressions, and coordinate care through appropriate referrals within the healthcare system.[2]

Heterozygous familial hypobetalipoproteinemia (FHBL) is a rare lipoprotein metabolism disorder caused by heterozygous mutations in the MTTP and apoB genes.[5] In most cases, patients are asymptomatic, and the condition is detected either incidentally through lipid profiling or during family screening of patients with homozygous abetalipoproteinemia.[5] Except for certain specific mutations, most individuals with FHBL have a reduced risk of atherosclerosis.[3] These patients generally do not require initial assessment or continuous follow-up. However, in many cases, LDL cholesterol levels may be one-third to one-fourth of normal, and mild deficiencies of fat-soluble vitamins may develop over time. Hepatic steatosis and, less frequently, severe liver complications may develop.[4,7]

Therefore, patients with extremely low levels of apoB-containing lipoproteins should be monitored regularly.[9] Initial evaluation and follow-up should include assessment of fat-soluble vitamin levels, hepatobiliary ultrasonography, and liver function tests. In cases with vitamin deficiencies, treatment is typically initiated at near-daily doses, without the need for high doses, and adjustments are made based on biochemical responses. In addition, the presence of metabolic comorbidities such as obesity and type 2 diabetes in patients with heterozygous FHBL may contribute to the development of hepatic fibrosis.[3,6]

## Case Report

A 37-year-old male patient presented to the family medicine outpatient clinic for a periodic health examination, without any active complaints. He reported no history of smoking or alcohol use. His family history was unremarkable. His height was 186 cm, weight 113 kg, and body mass index (BMI) was calculated as 32.7 kg/m$^2$ (obesity class I). His blood pressure was 127/68 mmHg, and his heart rate was 76 bpm. Physical examination findings were within normal limits.

The patient provided a fasting blood sample after approximately 8 hours of fasting. Laboratory results revealed markedly low LDL and total cholesterol levels, and elevated triglycerides. To exclude possible laboratory error and perform further testing, the patient was invited again to give another blood sample after an 8-hour fast. Additionally, abdominal ultrasonography revealed grade 1–2 hepatic steatosis. The biochemical parameters from the two separate fasting blood samples are summarised in Tables 1 and 2.

**Table 1.** First Laboratory Results (18.02.2025)

| Laboratory Parameter | Value | Unit | Reference Range |
|---|---|---|---|
| **Glucose** | 82 | mg/dL | 70 - 99 |
| **Urea** | 39 | mg/dL | 19 - 49 |
| **Creatinine** | 1.09 | mg/dL | 0.7 - 1.3 |
| **AST** | 32 | U/L | < 35 |
| **ALT** | 64 | U/L | < 50 |
| **LDH** | 164 | U/L | 120 - 246 |
| **Total Cholesterol** | 81 | mg/dL | < 200 |
| **Triglycerides** | 245 | mg/dL | < 150 |
| **HDL** | 23 | mg/dL | > 40 |
| **LDL** | 9 | mg/dL | < 100 |
| **VLDL** | 49 | mg/dL | 10 - 40 |
| **TSH** | 1.2 | µIU/mL | 0.55 - 4.78 |
| **Ferritin** | 47 | ng/mL | 22 - 322 |
| **Vitamin B12** | 214 | pg/mL | 211 - 911 |
| **Vitamin D** | 12 | ng/mL | 30 - 100 |

*Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; TSH, thyroid-stimulating hormone.*

**Table 2.** Second Laboratory Results (25.02.2025)

| Laboratory Parameter | Value | Unit | Reference Range |
|---|---|---|---|
| **Glucose** | 87.0 | mg/dL | 70 - 99 |
| **Urea** | 34.0 | mg/dL | 19 - 49 |
| **Creatinine** | 1.13 | mg/dL | 0.7 - 1.3 |
| **AST** | 42.0 | U/L | < 35 |
| **ALT** | 79.0 | U/L | < 50 |
| **LDH** | 205.0 | U/L | 120 - 246 |
| **Total Cholesterol** | 88.0 | mg/dL | < 200 |
| **Triglycerides** | 222.0 | mg/dL | < 150 |
| **HDL** | 24.0 | mg/dL | > 40 |
| **LDL** | 20.0 | mg/dL | < 100 |
| **VLDL** | 44.0 | mg/dL | 10 - 40 |
| **HbA1c** | 5.5 | % | < 5.7 |
| **Apolipoprotein B** | 51.0 | mg/dL | 66 - 144 |
| **INR** | 1.0 | - | 0.8 - 1.2 |
| **GGT** | 62.0 | U/L | < 73 |
| **ALP** | 101.0 | U/L | 53 - 128 |
| **Albumin** | 48.0 | g/L | 32 - 48 |
| **Total Protein** | 89.0 | g/L | 57 - 82 |

*Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; TSH, thyroid-stimulating hormone; INR, international normalized ratio; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.*

## Discussion

Hypocholesterolemia is a laboratory finding that is often overlooked, yet it may indicate underlying significant conditions.[8] Once secondary causes are excluded, primary hypolipidemic disorders should be considered, especially in cases with markedly low LDL and total cholesterol levels. In this case, periodic screening in an asymptomatic individual revealed significantly low lipid levels, leading to a presumptive diagnosis of heterozygous familial hypobetalipoproteinemia.

FHBL is an autosomal dominant lipid disorder caused most often by heterozygous mutations in the apoB gene. In affected individuals, LDL cholesterol levels may be reduced to one-third or one-fourth of normal values. Most patients are asymptomatic and diagnosed incidentally through lipid screening.[3] Although atherosclerosis risk is generally reduced in FHBL, the condition may be mistakenly regarded as benign. However, hepatic steatosis and, albeit rarely, progressive liver disease have been reported in some cases.[3,4]

In our case, abdominal ultrasonography revealed grade 1–2 hepatic steatosis, along with mild elevations in liver enzymes. These findings are consistent with the literature. According to the 2023 guidelines of the Turkish Society of Endocrinology and Metabolism, patients with FHBL should undergo assessment of fat-soluble vitamin levels, hepatobiliary ultrasonography, and liver function tests.[3] The presence of metabolic comorbidities such as obesity and type 2 diabetes mellitus may further contribute to the development of hepatic fibrosis in these individuals.[6] Given the patient's obesity and hepatic steatosis, the clinical picture was initially consistent with the recently updated definition of Metabolically Dysregulated-Associated Steatotic Liver Disease (MASLD). However, the incidental finding of profound hypocholesterolemia distinguished this case from typical MASLD, redirecting the diagnosis towards a primary lipid disorder such as FHBL. Evaluating such patients with awareness of MASLD criteria is crucial to identify metabolic risks; however, rare genetic etiologies must not be overlooked.

This case demonstrates that periodic examinations may reveal rare metabolic disorders even in asymptomatic individuals. Family physicians are equipped to assess the clinical context of laboratory findings and to make appropriate referrals based on preliminary diagnoses. In family medicine practice, instead of evaluating the patient solely based on complaints, conducting comprehensive periodic examinations and basic biochemical tests is important both for individual health and in terms of societal healthcare costs.

Family medicine is a continuous and holistic discipline that supports individuals not only in times of illness but also during periods of health. Family physicians provide guidance not only in disease prevention but also in helping patients understand their conditions, access reliable health information, and maintain healthy behaviours. In this context, they play a key role in the management of rare diseases by empowering patients to actively participate in their own care. As emphasised by the World Organisation of Family Doctors (WONCA), the role of the family physician extends beyond clinical intervention to include patient-centred education, behavioural support, and ongoing guidance within the healthcare system.[10]

Periodic health examinations in family medicine outpatient clinics provide an important opportunity for the early detection of serious metabolic disturbances, even in individuals without symptoms. This case exemplifies the recognition of a rare lipid disorder at the primary care level and its appropriate referral to a specialised department. Family physicians serve not only as the initial point of contact in the healthcare system but also hold a critical role in establishing preliminary diagnoses, performing holistic assessments, and ensuring timely specialist referrals.

**Ethical Considerations:** Written informed consent was obtained from the patient, and all personal information has been kept confidential.

**Conflict of Interest:** The authors declare no conflict of interest.

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